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Original Communications

I. INTRAVASCULAR CLOTTING AND AFIBRINOGENEMIA, THE PRESUMPTIVE LETHAL FACTORS IN THE SYNDROME OF AMNIOTIC FLUID EMBOLISM*

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IN 1941, Steiner and Lushbaugh[1] described the syndrome of amniotic fluid embolism which they considered the major cause of maternal death during labor. The chief clinical signs were dyspnea and sudden shock, and death was ascribed to the embolic effects of amniotic fluid and an associated anaphylactoid reaction. Widespread embolization of the pulmonary arterioles and capillaries by particulate matter contained in amniotic fluid were believed to be responsible for the essential pathologic lesions. The predisposing factors in the causation of this syndrome seemed to be tetanic uterine contractions, multiparity, and exceedingly large infants.

Since the original description of amniotic fluid embolism, additional cases of the syndrome have been recognized and reported.[2] As in the case of Steiner and Lushbaugh's patients, some died undelivered with the classical signs and symptoms of embolism, while others who survived the initial shock succumbed within one to three hours after delivery. In the latter group, bleeding from the mucous membranes and organ surfaces was noted, and some degree of vaginal bleeding was described which was attributed to atony of the uterus, secondary to shock. When these fatal cases are reviewed, two unexplained observations stand out. One is to the effect that the amount of mechanical blockage of the pulmonary vessels by amniotic debris is hardly suf-

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ficient to be the cause of death in every instance. Two, the comment is made that the blood is liquid at postmortem and clotting of any degree is rarely seen. One must hasten to add that such a finding may occur in sudden death regardless of cause.[3] The in vitro lysis of blood clots has recently been demonstrated by Green and Stoner.[4] The cause of death in this syndrome, therefore, appears not to be explained in all cases by the effects of embolism alone. Moreover, it is not clear why patients with amniotic fluid embolism, should they survive their original vascular insult, develop hemorrhagic manifestations.

Early in the course of a study of the coagulation mechanism in pregnancy at the Boston Lying-in Hospital, the records of a number of patients who died with unusual and uncontrolled hemorrhage were carefully reviewed. The purpose of this search was to uncover cases in which the hemorrhage might have been related to a defect in blood clotting. It was recalled that at autopsy one of these patients was found to have suffered an amniotic fluid embolism. The patient's difficulties began with the usual symptoms of respiratory distress and shock. The impressive feature of her clinical course was the fact that the blood became incoagulable.

A consideration of these cases suggested that the presence of amniotic fluid in the systemic circulation might somehow be related to the coagulation difficulties. Accordingly, a large number of samples of amniotic fluid were studied to determine whether this medium might contain some specific activity which could be responsible both for the initial shock of amniotic fluid embolism and the subsequent postpartum uterine and generalized hemorrhage.

It was demonstrated that uncontaminated amniotic fluid collected during labor contained a substance which behaved like thromboplastin. The fluid had the ability to reduce the clotting time of hemophiliac blood. While the coagulant activity of the samples of amniotic fluid differed somewhat, it could be substituted for commercial thromboplastin in the one-stage prothrombin test. Amniotic fluid was shown not to contain fibrinogen, thrombin, prothrombin, prothrombin accelerators, heparin, or fibrinolytic activity.[5] When amniotic fluid was injected into rabbits as in the original experiments of Steiner and Lushbaugh, thrombosis rather than mechanical embolism from amniotic debris was observed.[6]

The presence of significant amounts of thromboplastin in the amniotic fluid suggested that death in this syndrome could be ascribed to causes other than mechanical blockage from amniotic fluid debris. The postulate was first offered by us[7] that death in this syndrome might result from either extensive intravascular clotting or subsequent postpartum hemorrhage. Death from hemorrhage was regarded as the result of an afibrinogenemia, the end result of the effect of extreme intravascular clotting. The postmortem absence of extensive intravascular clotting and the fluidity of the blood alluded to above are believed to be due to the effect of a fibrinolytic enzyme which can be demonstrated in the blood soon after sudden death. In the absence of a blood fibrinogen concentration necessary for effective hemostasis (100 to 150 mg. per cent or more), clot formation at the uteroplacental site would be deficient

and a lethal postpartum hemorrhage would eventuate. We[7] predicted that the detection of afibrinogenemia by the "clot observation test" and timely fibrinogen replacement in the form of Fraction I would prevent many maternal deaths in amniotic fluid embolism. The recent report[8] of a fatal case of amniotic fluid embolism where death was associated with fibrinogen depletion and uncontrolled postpartum hemorrhage is consistent with the postulate.

More recently, several clinical cases have been encountered which support the concept as outlined. The objection may be raised that, short of autopsy evidence, the diagnosis of amniotic fluid embolism cannot be confirmed. However, the patients to be reported upon did exhibit the clinical picture of amniotic fluid embolism and their signs and symptoms cannot be accounted for by any other known obstetrical entity. Furthermore, if the concept that amniotic fluid embolization is in essence a disease of defibrination, there are certain therapeutic aids which should be employed to ameliorate a syndrome previously considered hopeless. The following cases are briefly reported:

Case Histories

CASE 1.—Mrs. N. R., No. 1200 (Toronto, Canada), a 27-year-old para iii, gravida iv, with a normal prenatal course, was admitted at term, not in labor but with ruptured membranes of 48 hours' duration. The blood pressure, urine, physical and obstetrical examinations were normal. One minim of Pitocin was given intramuscularly shortly after admission and tumultuous labor ensued. After two hours of vigorous labor, the cervix was 6 cm. dilated. Suddenly, the patient collapsed, vomited once, turned gray, lost consciousness, and stopped breathing. The pulse was absent but irregular heartbeats could be heard at the apex. The blood pressure was unobtainable. The patient was maintained on artificial respiration and given stimulants. The respirations returned gradually but were Cheyne-Stokes in type for many minutes before becoming regular. The blood pressure rose slowly to normal within the hour and consciousness returned. Although labor resumed, the fetal heartbeat was now absent. The obstetrician stated that there was no clinical evidence of premature separation of the placenta. The uterus was relaxed between contractions and vaginal bleeding was absent. One and one-half hours after her collapse the patient was delivered of a stillborn infant who weighed approximately 3,600 grams. The pulse was 80 and the blood pressure 110/75 at the time of delivery. The placenta was described as normal and pathological changes consistent with premature separation were not demonstrable.

Soon after delivery the patient began to bleed vaginally. The uterus seemed well contracted, but bleeding continued and there was oozing from the episiotomy. The uterus and vagina were carefully explored, but no anatomical cause for the postpartum hemorrhage was revealed. The uterus and vagina were packed but bleeding reappeared. It was noted that the blood which had accumulated failed to clot. At this time a sample of blood was drawn from the antecubital vein and it, too, failed to clot. Investigation of the patient's blood revealed that it did not prevent normal blood from clotting. Moreover, when a minute amount of normal blood was added to the patient's blood a clot formed.

Ecchymoses began to appear over the body. The urine which was clear at the time of hospital entrance was now scanty and black, and the sediment contained many casts. Several transfusions had been administered, but the patient developed signs and symptoms of shock. Over the next fifteen hours 6,000 c.c. of blood was given but bleeding continued. While bleeding continued after this blood replacement, a small clot was seen for the first time in the sample of venous blood. In spite of massive transfusions the fibrinogen concentration of this sample was only 134 mg. per cent in contrast to normal values in pregnancy of over 300 mg. per cent.

Five Gm. of fibrinogen obtained by plane from the Blood Bank of the Boston Lying-in Hospital were infused rapidly. Following this, bleeding ceased, clot formation of venous blood was normal, and blood drawn two hours later had a fibrinogen concentration of 450 mg. per cent. There was moderate oliguria for forty-eight hours after which the convalescence was normal. The patient continued to make a satisfactory recovery and is now entirely well.

Comment.—This patient showed sudden collapse which, by exclusion of other causes, was thought to be due to amniotic fluid embolism. The blood became incoagulable and uterine hemorrhage was uncontrolled even after many transfusions of whole blood. The diagnosis of afibrinogenemia was suspected by the clot observation test[9] and substantiated by measurements of the blood fibrinogen concentration.

CASE 2.—Mrs. R. P., No. 1201 (Charity Hospital, New Orleans), was admitted at eight months' gestation with beginning irregular uterine contractions. On entrance, physical examination was negative except for a very large, tense abdomen due to hydramnios. On the second hospital day, 1,000 c.c. of amniotic fluid was withdrawn by amniotomy, following which the procedure was discontinued because bright blood was obtained. Shortly thereafter labor began. The membranes ruptured spontaneously after several hours of labor and almost immediately the patient developed sudden peripheral vascular collapse and became stuporous. There was no visible bleeding at that time. Within a few minutes the presenting part was at the introitus and an anencephalic stillborn infant was delivered spontaneously.

Vigorous vaginal bleeding ensued and in spite of blood transfusions and oxytocics the patient's condition failed to improve. Bleeding was constant from the vagina and atony of the uterus seemed not to be a factor. Despite replacement of 2,500 c.c. of blood, the patient remained in shock and in a stuporous state while uterine hemorrhage continued. A sample of venous blood at this time formed a tiny inadequate blood clot. An analysis of a simultaneous oxalated sample showed the quantitative fibrinogen concentration to be 56 mg. per cent. Accordingly, the diagnosis of afibrinogenemia was made. Four Gm. of fibrinogen were infused quickly. Bleeding ceased, and the venous blood sample now formed an adequate, large clot. The subsequent clinical course was uneventful.

Comment.—This patient also showed sudden collapse, with shock and stupor consistent with amniotic fluid embolism. Whether the amniotomy allowed amniotic fluid to seep between the fetal membranes and uterine wall is only conjectural. Severe postpartum hemorrhage due to a relatively afibrinogenemic state was uncontrolled until after the administration of 4 Gm. of fibrinogen.

CASE 3.—Mrs. J. N., No. 1202 (Quincy, Mass.), was a 35-year-old para v, gravida v, admitted for elective induction of labor. The membranes were artificially ruptured and Pitocin was administered to initiate labor. After a labor of ninety minutes' duration, the patient was delivered of a normal infant by outlet forceps. With delivery, the patient went into profound shock and became pulseless and "seemed dead." The shock seemed out of proportion to the apparent blood loss. The uterus and vagina were explored and the examination was negative except for a small vaginal laceration which was repaired easily. The uterus was packed but bleeding continued.

After three transfusions, the pulse remained at 120 and the blood pressure at 80/40. Uterine oozing continued and at this point an afibrinogenemic state was considered. The original sample of maternal venous blood which had been drawn for cross-matching when shock first appeared was now re-examined. It was almost completely lacking in clot formation. Accordingly ¼ pint of blood and 2.5 Gm. of fibrinogen were infused. Thereupon the bleeding stopped and the patient's condition improved.

Comment.—The clinical course of this patient seems more consistent with amniotic fluid embolism than with any other known obstetrical entity. She

suffered extreme vascular collapse with mottled cyanosis after a short and vigorous labor. Attention must be called to the tumultuous labor which followed the use of Pitocin.

CASE 4.—Mrs. G. B., No. 1203 (Providence, R. I.), was a 24-year-old para i, gravida ii, whose prenatal course was complicated by a twin pregnancy. She developed pre-eclampsia with a trace of albumin in the urine and a blood pressure of 150/90 during the last month of pregnancy. The patient was admitted at term, not in labor, with ruptured membranes. The vertex was floating and the cervix only 2 cm. dilated. Intravenous Pitocin was administered and after a forceful two-hour labor the patient was delivered.

The first twin was delivered by low forceps, while twin No. 2 was delivered by version and extraction with some difficulty. The patient lost an estimated 700 c.c. of blood at the time of delivery. Although the uterus was firmly contracted, profuse vaginal bleeding occurred and the patient went into deep shock. Transfusions were started. An exploration of the generative tract for retained tissue or lacerations was entirely negative. The interior of both cervical lips bled freely and there were frequent gushes from the uterine cavity and the episiotomy. The pulse rose to 166 and the blood pressure was unobtainable, in spite of multiple transfusions.

Examination of the blood sample which had been drawn for cross-matching when hemorrhage first became apparent revealed complete lack of clot formation and suggested the diagnosis of afibrinogenemia. The patient's plasma contained 138 mg. per cent fibrinogen. This fibrinogen value was obtained from a blood sample taken after three transfusions indicating a probable pre-transfusion level of below 100 mg. per cent. Five hours after delivery vaginal bleeding continued and the patient had received her fifth transfusion. At this time, 2 Gm. of fibrinogen were injected, following which uterine hemorrhage ceased. Now for the first time a large stable clot formed in a freshly drawn specimen of venous blood. The patient did well thereafter.

Comment.—This case is presented as a possible variant of amniotic fluid embolism, for some of the signs and symptoms described for this condition were absent. The relationship between the short vigorous labor and the appearance of shock cannot be ignored. Also, the intrauterine manipulation necessitated by the version operation may have traumatized the placenta and decidua to the extent that thromboplastic material was introduced into the uterine sinusoids.

CASE 5.—Mrs. L. B., No. 1204 (Portland, Maine), a 29-year-old para ii, gravida iii, whose previous obstetrical history and prenatal course were normal, was admitted at term with ruptured membranes. After two hours of labor the patient suddenly became cyanotic and had a mild convulsion. Profound shock supervened with a weak and thready pulse after this episode. Coramine and oxygen were administered with a gradual return of the blood pressure to 110 mm. Hg systolic. However, the pulse remained at 136 and petechial hemorrhages appeared on the skin of the abdomen.

One hour later the patient was delivered of a stillborn infant. The placenta was expressed and appeared intact. However, the uterus bled steadily and there were intermittent gushes of liquid blood which failed to clot. The uterus was packed while plasma and then whole-blood transfusions were administered. The patient began to bleed from the nose and mouth and developed ecchymoses about the vulva. Respirations became shallow and the pulse exceedingly rapid, and the blood pressure could not be obtained. The patient died two hours after delivery of shock and hemorrhage. A sample of venous blood taken at the time of delivery remained unclotted for an observed sixteen hours. The addition of thrombin to a venous sample failed to produce a fibrin clot.

The noteworthy findings at autopsy included marked congestion of both lungs. Squamae were present in many of the capillaries and in some of the arterioles and veins of the lungs, findings consistent with amniotic fluid embolism (Fig. 1).*

*The gross and microscopic findings of this case were reviewed by Dr. Arthur T. Hertig in the Pathological Laboratories of the Boston Lying-in Hospital. The case is reported through the courtesy of Drs. F. M. Dooley and G. C. Leary.[10]

Comment.—Premature rupture of membranes, vigorous labor, cyanosis, and anoxic convulsion is the typical sequence of events in patients who develop an amniotic fluid embolism. This patient survived the initial shock only to develop an exsanguinating postpartum hemorrhage presumably because of an afibrinogenemia. The diagnosis of incoagulable blood was established at the time of delivery and a fibrinogen infusion would have restored normal hemostasis and possibly saved the patient's life.

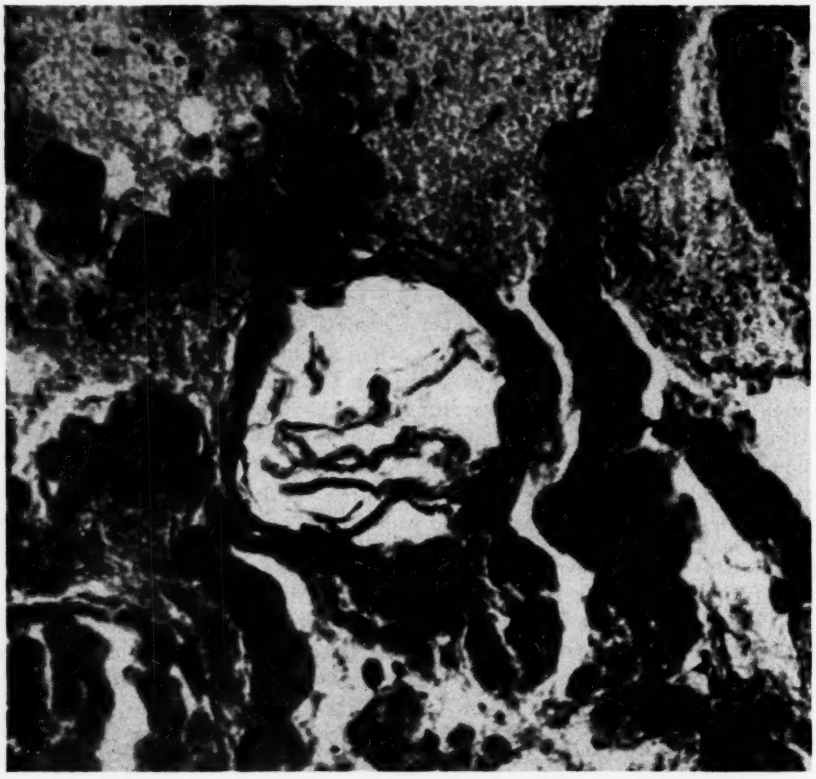

Fig. 1 (Case 5).—Photomicrograph of lung showing squamous cells in dilated capillary of lung. The cells are cut in cross section and appear as irregular wavy membranes surrounded by clear spaces. The capillaries in this region are congested and filled with red blood cells. The alveolar spaces contain a granular protein precipitate indicating pulmonary edema. (×400.)

Comment

With some justification there has been hesitancy in accepting the syndrome of amniotic fluid embolism as a definite entity. It is difficult to conceive that death of an anaphylactoid nature could occur during the physiological process of reproduction. The diagnosis of amniotic fluid embolism is rather frequently made when sudden obstetrical death occurs. In such circumstances, faulty anesthesia or cardiac failure has been shown on more than one occasion to be the true cause of death. Further, many pathologists find it difficult to correlate the findings in the lungs, which are often minimal, with a respiratory form of death.

The sequential changes which occur in this syndrome are understandable, however, if one considers that amniotic fluid has a thromboplastic effect. It has long been known that when a near-pure preparation of thromboplastin is

infused rapidly intravenously into dogs and cats, death soon follows but if administered slowly the animal will survive and defibrination of the blood will occur.[11, 12, 13] As with a slow infusion of thromboplastic preparation into the experimental animal, the introduction of amniotic fluid into the maternal blood stream may cause a state of incoagulable blood to develop. Assuming this comparison to be valid, the term amniotic fluid embolism is hardly descriptive, but rather the syndrome might better be referred to as "amniotic fluid infusion." Such a term would indicate more clearly the resultant physiological effects and avoid the concept that death is entirely the result of mechanical blockage of the pulmonary arteries by amniotic debris.

Considerable thromboplastin is required experimentally to defibrinate the dog.[13] One must presume, therefore, that if the amniotic fluid which enters the systemic circulation is capable of defibrinating the patient, it must contain considerable amounts of thromboplastin. The thromboplastin content of the fluid within the amnion will depend on the amount of tissue derived from fetal exfoliation and will obviously vary in its potency from patient to patient. Once the fluid gains access to the area between the chorion and the myometrium it will presumably acquire additional thromboplastin from the surrounding decidua, a tissue reported to have appreciable amounts.[14] The amniotic fluid which enters the venous sinusoids most probably will contain thromboplastin in a much higher concentration than in its original state.

The fact that the syndrome occurs in the majority of instances near the end of the first stage of labor suggests that a certain set of circumstances is needed for its development. These include both an available portal of escape and the forceful ejection of the amniotic fluid from the uterus. With respect to avenues of entrance of amniotic fluid into the maternal circulation there are two possibilities. The commonly accepted manner involves a rupture of the membranes somewhere in the upper segment of the uterus, with eventual escape of the fluid through the uteroplacental site.

One manner by which amniotic fluid may escape from the uterus into the maternal circulation has been well demonstrated.[15, 16] Amniotic squamous cells have been identified between the amnion and chorion, in the placental margin, the decidual sinusoids, and myometrial veins. Following rupture of the fetal membranes, the amniotic fluid may dissect between them and the uterine wall and in rare instances reach the placental margin to enter the venous sinusoids and the systemic circulation. The process is apparently expedited through the influence of vigorous uterine contractions. The escape of the fluid from the uterus is enhanced by those conditions in which the uterine vessels are opened abnormally, as in rupture of the uterus, cesarean section, marginal separation of the placenta, and normal separation with partial placenta accreta.[16] Where amniotic fluid was observed in the decidual sinusoids in one study there was microscopic evidence of premature separation and it was suggested that such a circumstance, by directly exposing the venous sinusoids, offered a ready portal for the entrance of amniotic fluid into the maternal circulation.[15]

The second and undoubtedly the more frequent outlet for the fluid is through the endocervical veins. These blood channels become lacerated during normal labor and account for the appearance of "bloody show." The upper portion of the cervix is thought to be incorporated in the lower uterine segment prior to or during labor. Some of the endocervical veins are thus included in the lower uterine segment and would not be covered by the fetal membranes unless the latter remained intact until the presenting part had traversed the completely dilated cervix. Should the membranes rupture prior to labor, the distal portion of the lower segment might become devoid of fetal membranes and allow the amniotic fluid to come into contact with the myometrium. Were the fetal vertex to tamponade the cervix, intrauterine pressure might increase sufficiently as the result of tumultuous labor to allow the trapped fluid to enter the uncovered endocervical veins of the lower uterine segment.

The eventual clinical course of the patient will be governed by the concentration of thromboplastin in the amniotic fluid and the rate and amount of autoinfusion of the latter. As in the experimental animal when large amounts of thromboplastic material are introduced suddenly into the blood stream, the resultant intravascular coagulation will lead to sudden death. However, when the amniotic fluid enters more slowly and over a longer period of time it is postulated in the human being, based on experimental evidence, that the blood will become defibrinated. While hemorrhage in the defibrinated experimental animal occurs only after trauma, in the obstetrical patient an already open wound is available, namely, the placental site. In the presence of a clotting defect, arterial and venous decidual vessels will fail to thrombose and uncontrolled bleeding will ensue.

Fibrinolytic activity has recently been reported in a fatal case of amniotic fluid embolism associated with afibrinogenemia.[8] A circulating fibrinolysin has also been observed in a patient with presumptive amniotic fluid embolism who recovered following fibrinogen replacement.[17] The presence of the enzyme is interpreted as the body's response to the extreme fibrin deposition associated with intravascular clotting.

In the recent fatal case reported by Ratnoff and Vosburgh[8] referred to above, antithrombin activity was also observed. The substance is demonstrated when thromboplastin is infused into the experimental animal, but disappears with the cessation of the administration of the coagulant.[13] While antithrombin is said not to interfere with fibrinogen formation or coagulation,[18] the presence of this inhibitor also may represent the body's attempt to defend itself against abnormal intravascular clotting. The ready formation of a clot after fibrinogen administration indicates that a possible prothrombin or Ac-globulin deficiency or a marked heparin or antithrombin activity is of secondary importance in producing defective hemostasis. It must be emphasized that the primary defect is a low concentration of circulating fibrinogen. This may be readily restored by the administration of Fraction I while any secondary alterations in the clotting mechanism are corrected by the use of fresh whole blood transfusions.

The predisposing factors which influence the production of the syndrome described by Steiner and Lushbaugh were applicable to the cases here reported. The most significant was tumultuous and exceedingly rapid labor. The question must therefore be raised whether the use of pituitary preparations may contribute toward the production of amniotic fluid infusion through the medium of vigorous labor. Such an effect was observed in the cases herein reported and in other cases of amniotic fluid embolism with which we are familiar. The use of pituitary extract for the convenience of shortening an otherwise normal labor must be challenged. The routine use of oxytocic drugs with the intent of reducing the latent period following artificial rupture of the membranes for therapeutic or elective induction of labor is equally hazardous and we believe should be condemned. Rarely will the drug be necessary under these circumstances. Superimposing the contractile effect of the drug on the uterus about to enter labor or already in effective labor may increase the frequency of amniotic fluid infusion by producing tetanic uterine contractions. The careless use of pituitary extract may, therefore, precipitate amniotic fluid infusion syndrome.

The treatment of amniotic fluid embolism encompasses preventive, supportive, and definitive therapy. The assumption that the disease is invariably fatal creates in the mind of the physician the belief that any treatment is futile. While a certain number of patients with this condition will die, we are of the opinion that prompt and energetic treatment will allow some to survive. In the event of a large infusion of amniotic fluid, death often follows within half an hour after the onset of symptoms. In the interim the treatment is directed toward the relief of cyanosis, apnea, and shock. Even in the apparently hopeless case the patient will occasionally rally, and here the treatment may be rewarding. In these patients, the treatment must be directed toward prevention of death from eventual postpartum hemorrhage.

Recovery will ultimately depend upon the restoration and maintenance of normal blood volume. In addition to adequate blood replacement, the treatment must include without undue delay the restoration of normal blood fibrinogen concentrations by the administration of fibrinogen (Cohn's Fraction I).*

The amount of fibrinogen required should be equivalent to that contained in the circulating blood (8 to 12 Gm.) for theoretically complete defibrination is possible. A minimum of 4 Gm. is necessary, but possibly three times this amount might be required before normal hemostasis will be restored.

Conclusions

The syndrome of amniotic fluid embolism, while admittedly rare, is a definite entity and a cause of death in the intrapartum period. With the realization that patients with amniotic fluid infusion (embolism) may die from hemorrhage as well as from respiratory distress, it is believed that the syn-

*The treatment might theoretically include an antiproteolytic trypsin inhibitor to neutralize any residual fibrinolytic activity which might be present.[19] Furthermore, on theoretical grounds, the known antagonistic action between heparin and thromboplastin suggests that carefully controlled administration of this anticoagulant might be of some therapeutic value in preventing further intravascular clotting. The use of anticoagulants and antifibrinolytic substances remains untested and their toxicity must not be minimized.

drome will be recognized more frequently than it has in the past. Especially should this apply if a careful search is made at autopsy for evidence of amniotic fluid debris in the lungs of those individuals who die of shock and blood loss commonly attributed to uterine atony and ruptured uterus.

The concept has been previously proposed that the clinical course and death in amniotic fluid embolism are due to intravascular clotting and defibrination.[7] This process is regarded as being initiated by the coagulant activity in the amniotic fluid should it gain entrance into the maternal circulation. The term "amniotic fluid infusion" rather than "embolism" would best describe the syndrome since the basic insult is believed to be intravascular clotting. The extent of intravascular clotting and defibrination will determine whether the patient will die immediately or will recover temporarily and if not properly treated will succumb within a few hours from postpartum hemorrhage. It is proposed that the delayed death is due to incoagulable blood resulting from afibrinogenemia. This will be corrected by the administration of adequate amount of fibrinogen and fresh whole blood.

Five patients with presumptive amniotic fluid infusion and subsequent incoagulable blood have been presented. Four of these were treated by fibrinogen replacement therapy and blood transfusions with recovery.

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II. INCOAGULABLE BLOOD IN SEVERE PREMATURE SEPARATION OF THE PLACENTA: A METHOD OF MANAGEMENT*

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PREMATURE separation of the normally implanted placenta, when it occurs in the severe form, has the dubious distinction of being the obstetrical complication with the greatest maternal risk. While the factors which contribute to the condition and the pathological changes both in the uterus and the body generally are well recognized, the precipitating cause of premature separation remains to be elucidated. Death may, on occasion, occur subsequently to renal and pituitary damage, but the vast majority of patients who succumb from premature separation do so directly from shock associated with uterine hemorrhage. Indeed, the kidney and the pituitary changes are largely the results of hemorrhagic shock.

The prevention of death and complications arising from hemorrhage in premature separation of the placenta has been approached mainly from the standpoint of the method of delivery. Controversy still continues as to whether the abdominal or pelvic method is the safer procedure for delivery, particularly in those patients in whom the placental separation is extensive.

Until 1933 the preferred treatment of severe premature separation of the placenta at the Boston Lying-in Hospital was cesarean section. At that time a review of 42 consecutive patients with extensive placental detachment treated by this method revealed a maternal mortality of 21 per cent.[1] A number of the patients died at or within hours of delivery undoubtedly from the effects of hemorrhage and shock. Certainly, by present-day standards they received inadequate amounts of blood replacement. An occasional patient survived 1 to 2 days with an associated anuria, and while death was ascribed to renal failure, hemorrhagic shock unquestionably was the major cause. When death did occur from uremia, characteristically in the second week following delivery, the available autopsy material revealed a nephrosis which could now be regarded as consistent with an ischemuric episode.[2] While not present in this particular series, it is recognized that in severe premature separation of the placenta, bilateral cortical necrosis of the kidney is on occasion responsible for death from renal failure. The exact mechanism by which these renal lesions develop is debatable and may be due to causes other than renal ischemia.

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In a later series reported from the same institution, the results were not appreciably different when cesarean section continued to be the method of delivery. This prompted Irving to discard abdominal delivery in cases in which the signs and symptoms were regarded as consistent with the severe form of the disease and to adopt and advocate as a routine method of delivery the so-called conservative treatment then in use at the Rotunda Hospital in Dublin. Irving further emphasized the distressing fact that, in his experience as well as in the literature, the death rate was highest in patients in whom cesarean hysterectomy was performed as a means of controlling the hemorrhage.[3] While the hemorrhage was attributed to atony, in retrospect it may have been due in some instances to a defect in the clotting mechanism.

The salient features of the so-called conservative method of treatment were induction of labor by artificial rupture of the membranes with or without cervical packing and eventual delivery through the pelvis. Excellent results had been reported in this country with this method of treatment,[4] and in the first group of patients treated by the conservative or nonoperative method at the Boston Lying-in Hospital the maternal mortality was extremely low.[3] While the mortality in patients with the severe forms of placental detachment so treated was no greater and in most instances lower than the rate obtained by cesarean section elsewhere, the accumulation of a greater number of cases indicated that factors other than the method of delivery were responsible for deaths. Some of the fatal cases treated by the conservative method were included in a report by Kellogg[5] in 1948. In general, the deaths occurred in undelivered patients who continued to demonstrate hemorrhagic tendencies and ineffectual labor. From these results and the personal experience of observing patients with severe premature separation die following cesarean hysterectomy, it was evident that an investigation regarding the coagulation mechanism in patients with obstetrical hemorrhage might prove profitable. The necessity of such a study was pointed up by the recent experience with one patient in this category with incoagulable blood who died in spite of thirty transfusions within an eight-hour period.

In 1948 this study was begun and involved several hundred patients with early and late pregnancy bleeding as well as those with postpartum hemorrhage. Included were patients with abortion, hydatidiform mole, placenta previa, and the mild, moderate and severe forms of premature separation. The following tests were performed on blood specimens from these patients: clotting test of Lee and White,[6] prothrombin by the one-stage method of Quick,[7] fibrinogen determinations,[8, 9] platelet counts,[10] tests for anticoagulant[11] and fibrinolytic activity.[12, 13, 14] These observations revealed alterations in blood clotting in severe cases of premature separation of the placenta. It was also demonstrated that the blood clotting was normal in patients with mild and moderate degrees of premature separation. A number of fortuitous observations were obtained which pointed to the fact that the loss of clotting power of the blood did not precede, but rather followed placental detachment.

The nature of the blood changes consisted of a reduction or at times a complete disappearance of circulating fibrinogen, some slight decrease in prothrombin concentration and, occasionally, especially before delivery, the ap-

pearance of a circulating fibrinolysin. In these studies the fibrinogen concentration of the blood was normal prior to and shortly following severe abruptio placentae. While the majority of these patients had some decrease in prothrombin concentration, the reduction never approached a hemorrhagic level. It appeared that the incoagulable state of the blood in premature separation of the placenta was not the result of hypoprothrombinemia. The adequacy of the prothrombin time indicated that components of the prothrombin complex which include the various accelerators (i.e., labile factor or Ac-globulin, etc.) do not play a decisive role in the production of incoagulable blood in severe premature separation. Accordingly, the incoagulable state of the blood was attributed to deficiency, in fibrinogen concentration. Afibrinogenemia (rather than hypofibrinogenemia or fibrinogenopenia) was the term selected to denote reduction in the circulating fibrinogen sufficient to cause faulty coagulation.

A simple clinical test was used to detect the defect in blood clotting in these cases. Failure of freshly drawn venous blood to clot or to form a normal-sized stable clot was believed sufficient evidence to conclude that the circulating blood fibrinogen had become reduced to a critical level incompatible with effective hemostasis. Subsequent fibrinogen determinations substantiated the conclusion. Further, hemostasis was considered inadequate if the clot when incubated at 37° C. dissolved within an hour. This latter effect was initially attributed to the presence of a fibrinolysin. It is now believed, however, that the failure to form a stable clot is possible under more than a single circumstance. *An unstable clot may form when the fibrinogen levels are in the range of the minimal values for hemostasis (100 to 150 mg. per cent),* or *in the presence of a fibrinolysin,* or *as a combined effect of both of these factors.* An unstable clot regardless of cause signifies that clinically there is ineffective hemostasis. The "clot observation test" was also recommended as a means of estimating the amount of fibrinogen therapy necessary to restore normal blood coagulation during labor and following delivery. It was demonstrated that if levels of fibrinogen and prothrombin were restored, normal hemostasis could be anticipated at the time of delivery. Further, it was believed that by means of fibrinogen therapy, an adequate circulating blood volume could be more readily maintained and renal and pituitary damage avoided. These findings were first presented in 1949[15] and since then the experience with a limited number of patients has been reported in subsequent papers.[16, 17, 18] The observations in these patients and in the case reported by Moloney[19] have subsequently been confirmed.[20-23]

Material

These reports stimulated interest in the detection and definitive treatment of incoagulable blood in premature separation of the placenta and requests for fibrinogen have been received from various areas of the country. Fibrinogen in limited amounts in the form of Cohn's Fraction I was available at the Boston Lying-in Hospital* and this blood fraction was distributed to other clinics on request. Through the cooperation of many physicians, clinical data

*This fraction was made available by Dr. Louis K. Diamond and was produced at the Massachusetts State Laboratory from plasma supplied by the American Red Cross.

TABLE I. PATIENTS WITH SEVERE PREMATURE SEPARATION OF THE PLACENTA AND AFIBRINOGENEMIA

PATIENT	FIBRINOGEN LEVEL BEFORE THERAPY (MG. %)	FIBRINOGEN ADMINISTERED (GM.)	BLOOD ADMINISTERED (C.C.)	FETUS	METHOD OF DELIVERY	OUTCOME AND COMMENT
Case 1.— Mrs. D. V. No. 1205	0	10	3,000	Dead	Section	Alive. Section for inertia 4 hours after amniotomy and fibrinogen restoration to 206 mg. %
Case 2.— Mrs. F. No. 1206	0	12	1,500	Dead	Section	Alive. Section for inertia 8 hours after amniotomy and fibrinogen restoration to 300 mg. %
Case 3.— Mrs. W. No. 1207	50	3	1,000	Dead	Pelvic	Alive. Postpartum hemorrhage. Stopped with fibrinogen. Blood fibrinogen 125 mg. % after therapy
Case 4.— Mrs. J. D. No. 1208	118	4	1,500	Dead	Pelvic	Alive. Fibrinogen 214 mg. % after therapy. No postpartum bleeding
Case 5.— Mrs. H. M. No. 1209	0	8	1,500	Dead	Section	Alive. Fibrinogen 282 mg. % after therapy
Case 6.— Mrs. J. M. No. 1210	82	6	2,500	Died in 6 hours	Section	Alive. Section done for inertia 8 hours after amniotomy and fibrinogen restoration to 171 mg. %
Case 7.— Mrs. McH. No. 1211	150	0	1,500	Died in 12 hours	Section	Alive. Fibrinogen 356 mg. % on third postpartum day
Case 8.— Mrs. G. No. 1212	125	0	500	Dead	Pelvic	Alive. Spontaneous rise in fibrinogen to 213 mg. % during 30 hours from amniotomy to delivery
Case 9.— Mrs. C. No. 1213	0	4	1,500	Dead	Pelvic	Alive. Fibrinogen 188 mg. % at delivery; 343 mg. % on fourth postpartum day
Case 10.— Mrs. M. V. No. 1214	106	0	2,500	Dead	Pelvic	Alive. Marked postpartum oozing. Borderline hemostasis. Fibrinogen 200 mg. % on second postpartum day, 387 mg. % on third postpartum day. Anemia
Case 11.— Mrs. T. No. 1215	100	0	6,000	Dead	Pelvic	Alive. Marked postpartum oozing. Fibrinogen 113 mg. % at delivery, 250 mg. % 24 hours postpartum. Should have received fibrinogen therapy
Case 12.— Mrs. H. O. No. 1216	Less than 100	2.5	1,000	Dead	Pelvic	Alive. No postpartum bleeding after fibrinogen

TABLE I.—CONT'D

PATIENT	FIBRINOGEN LEVEL BEFORE THERAPY (MG. %)	FIBRINOGEN ADMINISTERED (GM.)	BLOOD ADMINISTERED (C.C.)	FETUS	METHOD OF DELIVERY	OUTCOME AND COMMENT
Case 13.— Mrs. E. C. No. 1217	144 after transfusion	0	1,500	Dead	Section	Alive. Marked post operative oozing and ecchymoses. Should have received fibrinogen therapy
Case 14.— Mrs. H. F. No. 1218	Less than 100	5	2,000	Dead	Pelvic	Alive. Postpartum hemorrhage not controlled with transfusions but with fibrinogen therapy
Case 15.— Mrs. D. K. No. 1219	Less than 100	5	1,000	Dead	Section	Alive. Nonclotting blood discovered at section. Bleeding controlled with fibrinogen
Case 16.— Mrs. L. H. No. 1220	Less than 100	5	2,000	Dead	Section	Alive. Hemorrhage at section not controlled by transfusions but immediate response to fibrinogen. Anemia
Case 17.— Mrs. A. S. No. 1221	Less than 100	5	500	Dead		Alive. Massive ecchymoses and hemorrhage from incisions and uterus 3 hours after section; controlled by fibrinogen. Anemia
Case 18.— Mrs. E. K. No. 1222	Less than 100	2.5	2,000	Dead	Pelvic	Alive. Profuse postpartum hemorrhage, not controlled by transfusion; responded to fibrinogen
Case 19.— Mrs. T. G. No. 1223	107	7.5	2,000	Dead	Section	Alive. Postoperative extensive ecchymoses and free hemorrhage not controlled by transfusion; responded to fibrinogen
Case 20.— Mrs. J. L. No. 1224	Less than 100	5	3,000	Dead	Pelvic	Alive. Postpartum hemorrhage not controlled by transfusion but by fibrinogen therapy. Fibrinogen 288 mg. % after therapy. Anemia
Case 21.— Mrs. P. No. 1225	85	2.5	8,000	Died in 5 minutes	Section	Alive. Postoperative hemorrhage not controlled by transfusion; responded to fibrinogen and simultaneous uterine artery ligation
Case 22.— Mrs. DeL. No. 1226	Less than 100	2.5	5,000	Dead	Section	Alive. Hysterectomy failed to control postpartum bleeding. Responded to fibrinogen 320 mg. % 24 hours postpartum
Case 23.— Mrs. R. E. No. 1227	175	2.5	1,500	Alive	Pelvic	Alive. Postpartum bleeding until fibrinogen given. Fibrinogen level 332 mg. % reached

TABLE I.—CONT'D

PATIENT	FIBRINOGEN LEVEL BEFORE THERAPY (MG. %)	FIBRINOGEN ADMINISTERED (GM.)	BLOOD ADMINISTERED (C.C.)	FETUS	METHOD OF DELIVERY	OUTCOME AND COMMENT
Case 24.— Mrs. D. C. No. 1228	Less than 100	5	500	Dead	Pelvic	Alive. Antepartum eclampsia with severe premature separation and afibrinogenemia. Anemia
Case 25.— Mrs. Bri No. 1229	128	2.5	0	Dead	Pelvic	Alive. Postpartum hemorrhage responded to fibrinogen therapy
Case 26.— Mrs. Sc. No. 1230	Less than 100	2.5	2,000	Dead	Section	Alive. Postpartum hemorrhage responded to fibrinogen therapy
Case 27.— Mrs. JAS No. 1231	Less than 100	5	1,000	Dead	Section	Alive. Bled after section. Should have received fibrinogen prior to operation
Case 28.— Mrs. K. C. No. 1232	0	5	2,000	Dead	Pelvic	Alive. Clot formation restored by fibrinogen. Uneventful pelvic delivery
Case 29.— Mrs. M. M. No. 1233	85	2.5	4,000	Alive	Pelvic	Alive. Postpartum hemorrhage not controlled until fibrinogen therapy. Fibrinogen 310 mg. % postpartum
Case 30.— Mrs. O. No. 1234	100	2.5	2,500	Dead	Pelvic	Alive. Uncontrolled postpartum hemorrhage until fibrinogen administered. Fibrinogen 192 mg. % in the puerperium
Case 31.— Mrs. M. K. No. 1235	Less than 100	2.5	1,500	Dead	Section	Alive. Postcesarean generalized bleeding not controlled until fibrinogen therapy
Case 32.— Mrs. J. M. No. 1236	Less than 100	2.5	1,000	Dead	Pelvic	Alive. Uncontrolled postpartum hemorrhage. Responded to fibrinogen therapy
Case 33.— Mrs. F. A. N. No. 1237	0	5	2,500	Dead	Section	Alive. Cesarean hysterectomy did not control hemorrhage. Immediate hemostasis with fibrinogen
Case 34.— Mrs. T. B. No. 1238	Less than 100	4	4,000	Dead	Pelvic	Alive. Postpartum hemorrhage. Responded to fibrinogen. After therapy fibrinogen 224 mg. %

and blood samples have been secured from 50 patients, the majority of whom received fibrinogen in the treatment of afibrinogenemia mainly for severe premature separation of the placenta. Other cases included amniotic fluid infusion and those with long-standing intrauterine death which are reported elsewhere.[24, 25] Over the past two years we have had further opportunity to observe and treat several patients with severe premature separation with coagulation defects at the Boston Lying-in Hospital and in surrounding community hospitals. A summary of cases with severe premature separation in whom data were sufficient is given in Table I.

It is the purpose of this paper to present the significant factors associated with noncoagulable blood in severe premature separation of the normally implanted placenta and to submit for consideration the policy of treatment of this condition now practiced at the Boston Lying-in Hospital. The following cases have been selected from the above group to illustrate the basis for such a policy.

CASE 1.—Mrs. D. V., No. 1205, was a 36-year-old para 0, gravida i, who was admitted to the Boston Lying-in Hospital at 36 weeks' gestation because of abdominal pain of two hours' duration. The patient's prenatal course had been uneventful with no evidence of toxemia. At admission the uterus was enlarged to the xiphoid and tense. The fetal heartbeat was absent. The pulse was 100 and the blood pressure 110/80. There was no external bleeding.

Soon after hospital entrance a sample of clotted blood was obtained (Fig. 1, tube 1). This blood clotted within a few minutes but was completely fluid after thirty minutes. No further clot could be formed by the addition of thrombin, although prompt clotting occurred when fibrinogen solution was added.

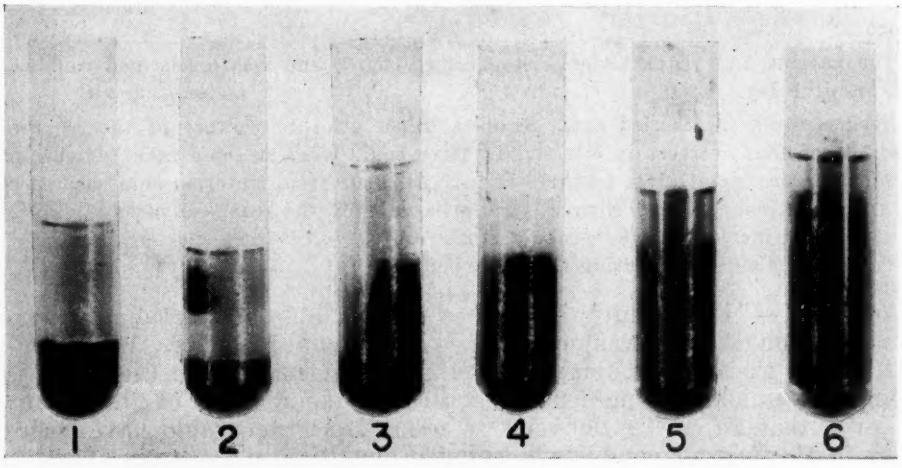

Fig. 1 (Case 1).—Blood clots in case of Mrs. D. V.
Tube 1, Soon after hospital admission.
Tube 2, After 2 Gm. fibrinogen and 500 c.c. blood (2 hours after admission).
Tube 3, After 8 Gm. fibrinogen and 1,000 c.c. blood (3½ hours after admission).
Tubes 4 and 5, Second and third hours after artificial rupture of membranes.
Tube 6, After 10 Gm. fibrinogen and 3,500 c.c. blood (1 hour after cesarean section).

Two hours after hospital entrance the patient had a sudden profuse hemorrhage from the uterus, estimated at 1,000 c.c. and bleeding continued in excessive amounts thereafter. It was obvious that her condition had become worse and she was now in moderate shock. Five hundred c.c. of blood and 2 Gm. of fibrinogen were administered quickly. Following this therapy a sample of venous blood clotted in ten minutes. The clot which was soft and jellylike decreased to one-eighth normal clot size within two hours but thereafter remained stable (Fig. 1, tube 2).

Vigorous replacement therapy was continued and by ninety minutes after the appearance of external bleeding 8 Gm. of fibrinogen and 1,000 c.c. of blood had been infused. Maternal venous blood now clotted in eight minutes and the clot which formed was large and smooth and of excellent consistency (Fig. 1, tube 3). The patient had stopped bleeding externally. The prothrombin time was 23.8 seconds with a control of 17 seconds and the fibrinogen 206 mg. per cent. Sterile pelvic examination revealed no evidence of placenta previa. Although the cervix was unfavorable for induction, membranes were artificially ruptured for it was judged worth while to see whether the patient would go into labor with small doses of Pitocin stimulation.

One hour after artificial rupture of the membranes venous blood formed an excellent clot, the fibrinogen concentration was 219 mg. per cent and the prothrombin time 21 seconds. The patient's condition remained good and hourly clot examinations (Fig. 1, tubes 4 and 5) showed a large stable clot. Meanwhile an additional 1,500 c.c. of blood was infused to replace prior blood loss.

Four hours after rupture of the membranes labor had not ensued. The patient was now in good condition and her coagulation mechanism had been restored. Since the patient was a primipara, a cesarean section was believed indicated. There was no guarantee that coagulation difficulties might not reappear if delivery was not accomplished within a few hours. Accordingly, a classical cesarean section was quickly done under inhalation anesthesia. The placenta was completely separated and the baby recently dead. There were large subserosal hemorrhages in the cornual areas of the uterus. There was an estimated 1,200 c.c. of clotted blood in the uterus. An additional 2 Gm. of fibrinogen and 1,000 c.c. of blood were given during the operation because the wound margins seemed to ooze excessively.

Venous blood taken one hour after surgery formed a large firm clot (Fig. 1, tube 6). The plasma fibrinogen concentration was now 256 mg. per cent and the prothrombin time 20 seconds.

The patient had an excellent postoperative course and was discharged well on the eighth hospital day.

Lysin tests were carried out. Samples taken prior to rupture of the membranes showed 30 per cent decrease in clot size in three hours whereas those taken after rupture of the membranes were intact in three hours. All tests from maternal sera secured prior to cesarean section produced complete disappearance of the standard plasma clots after twenty hours of incubation whereas the serum from a postcesarean specimen had no effect on the standard plasma clot during this same period.

Comment.—The patient's blood was incoagulable at the time of hospital entrance although there was no evidence of external bleeding. When the latter did occur there was a temporary clinical deterioration in the patient but bleeding was quickly brought under control by the addition of fibrinogen. It is believed that an earlier delivery by cesarean section would have been disastrous in the face of complete fibrinogen depletion at the time of entrance into the hospital. The criticism which seems more valid is the fact that there was considerable delay in instituting treatment. Earlier transfusion and rupture of the membranes would have aided materially in improving the status of the patient. From the experience with this patient we now know that a state of severe depletion of fibrinogen is amenable to correction with specific therapy. This fact emphasizes the importance of the restoration of the patient before any operative procedure is attempted. The lysin tests seemed indicative of the presence of an active fibrinolysin in the maternal blood stream following severe separation, less active after rupture of the membranes, and disappearing after delivery.

CASE 2.—Mrs. F., No. 1206, a 37-year-old para iii, gravida iv, whose three prior deliveries were uneventful, entered the hospital with brisk vaginal bleeding. During the present pregnancy her prenatal course was normal until the twenty-ninth week when she developed mild abdominal pain and while at home six hours later began to bleed profusely. The patient was admitted to the hospital directly thereafter with a clearly audible fetal heartbeat. There was a periodic discharge of dark liquid blood from the vagina and the systolic blood pressure was 80 mm. Hg and the pulse rapid. One and one-half hours after admission, the patient was examined under anesthesia. The cervix was thick, firm, and barely admitted one finger. There was no evidence of placenta previa and the diagnosis of premature separation of the placenta was made. The membranes were ruptured artificially and a course of Pitocin stimulation was administered.

At the time of rupture of the membranes a sample of venous blood (Fig. 2, tube 1) revealed no clotting. No fibrinogen was detected in the sample. After 2 Gm. of fibrinogen were given the circulating fibrinogen concentration was only 88 mg. per cent (Fig. 2, tube 2). The patient was vomiting bloody stomach contents. In addition marked ecchymoses appeared, particularly over the skin surfaces of the arms. Some four and one-half hours after rupture of the membranes, fibrinogen totaling 8 Gm. had been infused. together with 1,500 c.c. of blood. The patient's peripheral blood now formed an adequate clot and the quantitative fibrinogen was 180 mg. per cent (Fig. 2, tube 3). Because labor did not ensue, a cesarean section was done seven hours after rupture of the membranes and a stillborn premature infant delivered. Prior to cesarean section, 4 additional Gm. of fibrinogen were infused which raised the circulating fibrinogen concentration to 300 mg. per cent (Fig. 2, tubes 4 and 5). Blood fibrinogen four hours after cesarean section was 294 mg. per cent (Fig. 2, tube 6). The patient's postoperative course was satisfactory and she was discharged on the tenth postoperative day.

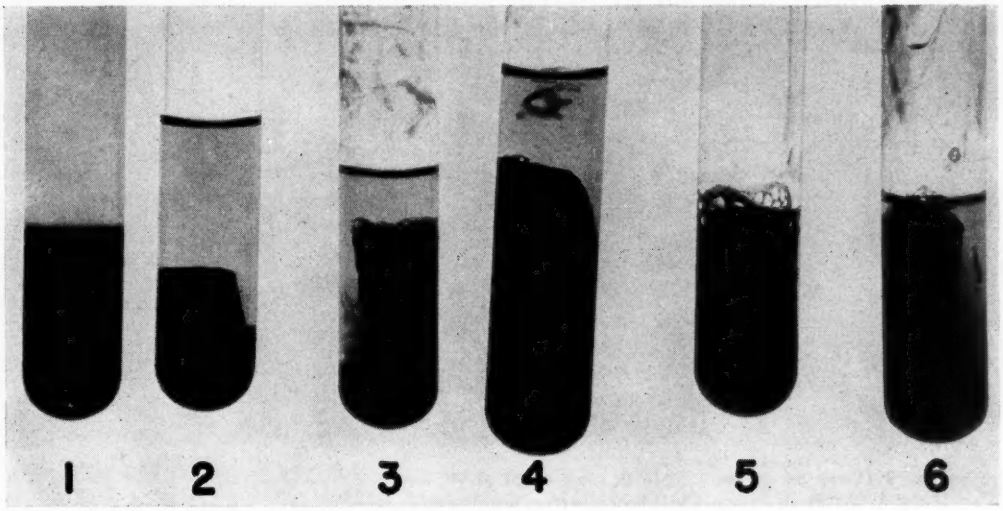

Fig. 2 (Case 2).—Blood clots in case of Mrs. F.

Tube 1, One and one-half hours after hospital admission and at the time of artificial rupture of the membranes.

Tube 2, After 2 Gm. fibrinogen.

Tube 3, After 8 Gm. fibrinogen and 1,500 c.c. blood (4½ hours after artificial rupture of the membranes).

Tubes 4 and 5, After 4 Gm. additional fibrinogen. Total 12 Gm. fibrinogen (7 hours after amniotomy).

Tube 6, Four hours after cesarean section.

Comment.—Spontaneous hemorrhages in various locations of the body were an outstanding feature of this patient's condition. Immediate cesarean section in the presence of severe nontoxic separation would have undoubtedly ended in a fatal hemorrhage.

CASE 3.—Mrs. W., No. 1207 (consultation case), a para iii, gravida iv, whose prenatal course was normal, entered a community hospital in active labor at term. The membranes were intact. The fetal heartbeat was absent and the uterus seemed firmer than normal between contractions. The patient was delivered of a nonmacerated stillborn infant two hours after hospital entrance together with the placenta and a large amount of old blood clot. Although the uterus contracted well, a heavy continuous postpartum hemorrhage followed delivery. The birth canal was examined and no anatomic reason for the bleeding was found. A sample of venous blood was drawn for cross-matching.

Although initial clotting occurred, within a short period of observation the clotted blood returned to a fluid state. A 500 c.c. transfusion was given. Nevertheless, a steady loss of blood continued from the uterus.

The patient was seen by one of us in consultation three hours after delivery. She was still bleeding and had received 1,000 c.c. of freshly drawn blood.

There was no clot in the original venous sample taken prior to the transfusions and the addition of thrombin did not produce clot formation (Fig. 3, tube 1). However, when fibrinogen solution was added, a large clot promptly formed. An analysis of this blood sample showed a plasma fibrinogen concentration of 50 mg. per cent. A clotted sample taken after 1,000 c.c. of blood formed a very small residual clot (Fig. 3, tube 2). The fibrinogen concentration was 81 mg. per cent.

Three Gm. of fibrinogen were infused within a fifteen-minute period. Uterine blood loss stopped immediately. Venous blood fibrinogen concentration was 125 mg. per cent and the peripheral blood clot was large and stable (Fig. 3, tube 3).

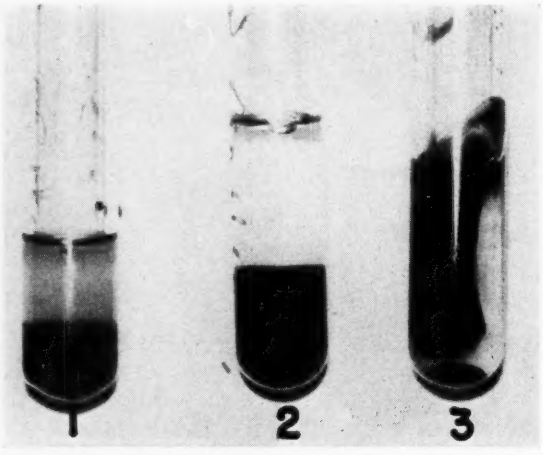

Fig. 3 (Case 3).—Blood clots in case of Mrs. W.
Tube 1, After delivery (2½ hours after admission).
Tube 2, After 1,000 c.c. blood (5 hours after admission).
Tube 3, After 3 Gm. fibrinogen (5½ hours after admission).

The one-stage prothrombin time was 80 seconds prior to transfusions. This value was influenced by the very low blood fibrinogen values. The prothrombin time after transfusion was 18 seconds (control of 15 seconds) and after fibrinogen therapy was 19 seconds. Since the patient continued to bleed after transfusion, it was interpreted that the elevation in prothrombin time was not the agent responsible for the hemorrhagic diathesis.

Comment.—The favorable response to a small amount of fibrinogen illustrates that the postpartum hemorrhage in this case was the result of deficiency in the clotting mechanism rather than uterine atony. This emphasizes that effective uterine hemostasis is dependent on thromboses of the spiral uteroplacental site vessels as well as uterine contractility.

CASE 4.—Mrs. J. D., No. 1208, was a 33-year-old para iv, gravida v, who entered the hospital because of increasingly severe abdominal pain and vaginal spotting of four hours' duration. The patient had had three previous separations of the placenta, two of which ended in stillbirths and required multiple transfusions. Her prenatal course in the pregnancy was normal until she was admitted at 26 weeks' gestation.

On entrance, the fetal heartbeat was absent and the uterus was tense, tender, and enlarged to the size of a 36 weeks' gestation. A sample of venous blood formed a poor

clot which underwent almost total liquefaction in thirty minutes (Fig. 4, tube 1). The blood pressure was 100/64, the pulse 92, and the urine contained 400 mg. per cent of albumin. The quantitative fibrinogen one hour after admission was 118 mg. per cent (Fig. 4, tube 2). Sterile vaginal examination revealed the cervix 3 cm. dilated and a vertex presentation. The membranes were artificially ruptured releasing pink-stained amniotic fluid. Two and one-half hours after admission, 4 Gm. of fibrinogen and 500 c.c. of blood were infused and a stable clot formed. The fibrinogen level was 214 mg. per cent (Fig. 4, tube 3). An additional 1,000 c.c. of blood was administered to replace the estimated blood loss. Some five hours before delivery the peripheral blood clot was excellent and remained so thereafter while the quantitative fibrinogen was 267 mg. per cent (Fig. 4, tube 4).

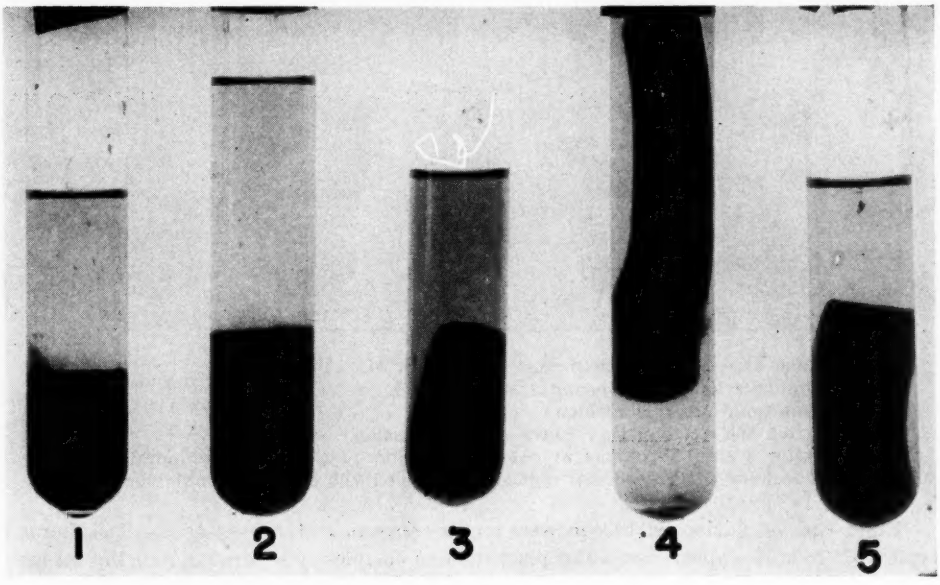

Fig. 4 (Case 4).—Blood clots in case of Mrs. J. D.
Tube 1, At the time of hospital admission.
Tube 2, One hour after admission.
Tube 3, After 4 Gm. fibrinogen and 500 c.c. blood (2½ hours after admission).
Tube 4, After additional 1,000 c.c. blood (4½ hours after admission).
Tube 5, Two hours after delivery.

A course of intramuscular Pitocin aided in the induction of labor and the patient was delivered spontaneously of a stillborn infant nine and one-half hours after admission. The placenta appeared completely separated and was accompanied by 1,500 c.c. of old liquid and clotted blood. There was no postpartum blood loss and the patient was discharged well on the eighth hospital day. Her blood clot during labor and two hours post delivery remained adequate (Fig. 4, tube 5).

CASE 5.— Mrs. H. M., No. 1209, was a 39-year-old para iii, gravida iv, who entered the hospital with abdominal pain which was intermittent and mild at first but became strong and regular after several hours and led to hospital admission. Her previous obstetrical history included three cesarean sections for cephalopelvic disproportion. The fetal heartbeat was present, the fundus was consistent with a 6 months' pregnancy and relaxed well between regular contractions. The blood pressure was 120/80.

One-half hour after admission the patient complained of constant severe abdominal pain and the blood pressure dropped to 80/50. For the first time some vaginal bleeding appeared. At this time the fetal heartbeat was lost, the uterus was tetanically contracted, and the diagnosis of severe premature separation of the placenta was made.

Five c.c. of venous blood was drawn to determine whether clot insufficiency was present. This specimen formed a soft, jelly clot which fragmented within twenty minutes, leaving the blood completely fluid (Fig. 5, tube 1). Fibrinogen was not detected in the plasma. Blood transfusion was started while fibrinogen was secured. An oxalated blood sample taken at this time was also devoid of fibrinogen (Fig. 5, tube 2). Four hours after admission 800 c.c. of blood had been administered, and clotting was still absent (Fig. 5, tube 3). The circulating fibrinogen level was only 16 mg. per cent. At this point the patient was actively bleeding from the mouth, nose, and vagina, and the uterus had increased to the size of a full-term pregnancy.

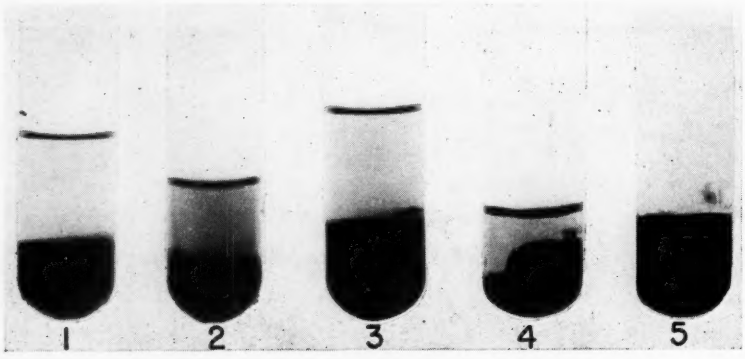

Fig. 5 (Case 5).—Blood clots in case of Mrs. H. M.
Tube 1, One-half hour after hospital admission.
Tube 2, One hour after admission.
Tube 3, After 800 c.c. blood (4 hours after admission).
Tube 4, After 8 Gm. fibrinogen at cesarean section (4½ hours after admission).
Tube 5, One hour after cesarean section. Received 700 c.c. additional blood.

Eight Gm. of fibrinogen was infused and a cesarean section was done. The uterus had a typical Couvelaire appearance. The placenta was completely separated, and the infant was stillborn. At the conclusion of the operation approximately four and one-half hours after admission, hemostasis was good, the peripheral blood clot was stable (Fig. 5, tube 4), and the fibrinogen level was 282 mg. per cent.

One hour after surgery the peripheral blood clot was adequate (Fig. 5, tube 5), and the fibrinogen level was 222 mg. per cent. While the patient received 1,500 c.c. of blood replacement she left the hospital on the eighth postoperative day with a rather marked anemia.

Comment.—Cases 4 and 5 illustrate that the severe type of placental separation with subsequent afibrinogenemia may appear even prior to the thirtieth week of pregnancy. In both instances separation was extensive in the absence of evident toxemia.

CASE 6.—Mrs. J. M., No. 1210, was a 30-year-old para 0, gravida iii, whose prenatal course was normal until the twenty-ninth week when she was admitted because of painless bleeding. The patient had had two previous miscarriages. Examination on entrance showed a soft uterus and the blood pressure was 110/70. The urine was negative. The presumptive diagnosis was placenta previa. Accordingly the patient was treated by bed rest for the first twelve hours after hospital admission.

At the end of this period vaginal bleeding reappeared. On re-examination the uterus was firm and failed to relax. Serial samples of venous blood were drawn at 6:00 P.M., 6:30 P.M., and 7:00 P.M. (Fig. 6, tubes 1, 2, 3). The diminution in clot size evident in the latter samples was diagnostic of a developing afibrinogenemia. This was verified by quantitative fibrinogen determinations; the value at 6:30 P.M. was 101 mg. per cent and at 7:00 P.M. 82 mg. per cent. The urinary albumin was now 1,000 mg. per cent and red cells were present.

The membranes were artificially ruptured at 7:30 P.M. and Pitocin stimulation started. Fibrinogen therapy was initiated. By 8:30 P.M. 6 Gm. had been infused, a stable clot formed (Fig. 6, tube 4), and the quantitative fibrinogen was 171 mg. per cent. Blood loss was restored with five transfusions.

The circulating fibrinogen remained adequate and the peripheral blood clot stable on repeated examinations during the next several hours (Fig. 6, tubes 5-8). At 4:00 A.M. labor had not ensued and therefore a cesarean section was performed without event. Two hours after hysterotomy the quantitative fibrinogen was 171 mg. per cent (Fig. 6, tube 9). The patient was discharged well on the tenth postoperative day.

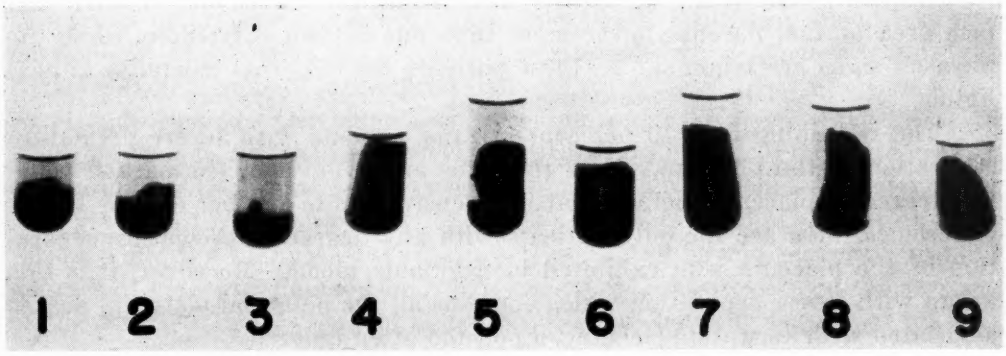

Fig. 6 (Case 6).—Blood clots in case of Mrs. J. M.
Tube 1, 6:00 P.M.
Tube 1, 6:00 P.M.
Tube 2, 6:30 P.M.
Tube 3, 7:00 P.M.
Tube 4, 8:30 P.M. After 6 Gm. fibrinogen and 2,500 c.c. blood.
Tube 5, 9:30 P.M.
Tube 6, 11:00 P.M.
Tube 7, 1:00 A.M.
Tube 8, 3:00 A.M.
Tube 9, 7:00 A.M. Two hours after hysterotomy.

Comment.—This case has many interesting and important features. The urine, blood pressure, and clot formation at hospital entrance were normal. At this time the tentative diagnosis was placenta previa. However, as a mild nontoxic separation became severe and clinically evident there was a concomitant decrease in blood fibrinogen concentration and the development of marked proteinuria. Had the patient been seen initially with this finding a diagnosis of so-called toxic separation might have been made. Finally, following artificial rupture of the membranes the clotting ability seemed to be more easily maintained.

Treatment

The method of management herein proposed is determined and conducted by the status of the clotting mechanism. The treatment is directed principally toward the detection and prompt correction of afibrinogenemia which in our opinion is the principal cause of uncontrolled hemorrhage and death in this syndrome. In the event the blood is rendered incoagulable by a critical reduction in fibrinogen concentration and the circumstance is disregarded, delivery by either the pelvic or the abdominal route will be attended by disaster.

The reader may ask with some justification, "Why has the problem of incoagulable blood in the management of premature separation of the placenta

been given so little attention?'' The answer in part seems to be that death from hemorrhage being regarded as preventable, fatalities in abruptio placentae are all too often attributed to pregnancy toxemia or renal failure. More important, the statistical approach obscures the significance of the patient with severe premature separation. In fact, 90 to 95 per cent of all patients with premature separation of the placenta have only mild to moderate degrees of placental detachment. Ofttimes clinical manifestations are absent and the diagnosis is made incidentally to routine pathological examination of the placenta.[26] In others the degree of separation involves only a small surface area of the placenta never more than one or two cotyledons while the physical signs are minimal. In these patients the maternal mortality is negligible.

The remaining 5 to 10 per cent are the patients with severe premature separation of the placenta. Here the signs and symptoms are marked while the degree of placental detachment is extensive (50 to 100 per cent). In our experience these are the only patients with any degree of premature separation of the placenta who exhibited incoagulable blood. Moreover, it is this group with severe separation which contains all the potential maternal deaths associated with abruptio placentae, a fact too often ignored.[5]

An evaluation of the degree and severity of the placenta separation is a prerequisite to treatment. In general the signs and symptoms and laboratory findings determine with fair accuracy the extent of the disease. Placental separation when it occurs in the mild or at most moderately severe form, is generally not accompanied by shock and if present is transient in character. The uterus is soft and relaxed and the fetal heartbeat is usually of good quality. If uterine tenderness is present, it is restricted to a small area. While the serosal covering of the uterus may show small localized areas of discoloration when seen at cesarean section, the myometrium is devoid of changes. The clinical course of the patient is in general benign and, while blood replacement is often needed, therapeutic response is entirely satisfactory.

By contrast, patients with severe premature separation some time in their course reveal shock which becomes extreme if not properly treated. In this group some variation in the normal values of the components of blood clotting can usually be demonstrated and in the majority of the cases the blood will become incoagulable. In these cases with severe separation, the fetal heartbeat is usually absent. The uterus by palpation is boardlike and tender. Morphologic alterations in the uterus responsible for these signs and symptoms have been most vividly described by Couvelaire who proposed the term uteroplacental apoplexy to identify these changes. Accumulation of blood beneath the peritoneal surface gives the uterus a mottled, discolored appearance, typical of the disease. Both grossly and microscopically the myometrial fibers are widely separated by the infiltration and extravasation of the retroplacental blood. On occasion one gains the impression that the depth of the shock seems out of proportion to the blood loss. Consequently, it is often stated that some unknown factor, perhaps a toxic substance derived from tissue trauma and destruction, is somehow responsible for the shock. It would seem unneces-

sary, however, to evoke reasons to explain the shock other than a decrease in blood volume and in general the magnitude of initial blood loss has not been appreciated. In addition to the concealed uterine hemorrhage, extravasation of blood into the broad ligaments and retroperitoneally through the lower abdomen may reach sizable proportions as observed at cesarean operation or determined by vaginal examination in the early puerperium. Clot volume represents only 40 per cent of the amount of blood shed. In many of the personally treated patients in this series, measured clot volume at the time of delivery was as much as 1,500 c.c. which indicates an intrauterine concealed blood loss of at least 2,500 c.c. The difficulty of estimating blood loss was particularly apparent in this series and subsequent iron deficiency anemia was common even in spite of large blood replacement.

In addition to classifying cases according to the severity of the separation it has become customary to categorize patients into toxic and nontoxic groups, depending on the presence or absence of pregnancy toxemia. The tendency is to view the toxic group as patients with the severe form of premature separation while the nontoxic patients are regarded as having moderate to mild degrees of placental detachment. It is our opinion, however, that the severity of the disease is not dependent so much on the presence or absence of toxemia per se, as on the extent of the separation. *The assumption is unwarranted that in the absence of demonstrable toxemia the patient's disease is necessarily mild. This is an important consideration with respect to treatment.*

With due regard for the individualization of patients, the syndrome of premature separation of the placenta is amenable to a policy of management. The preferred obstetrical treatment at the Boston Lying-in Hospital for the milder forms of premature separation of the placenta is induction of labor and pelvic delivery. Pelvic examination with artificial rupture of the membranes is performed as soon after hospital entrance as feasible. The patient is always examined in the operating room with preparations made for laparotomy should a placenta previa be encountered. In addition to initiating labor, the effect of rupture of the membranes seems to be to deter further placental separation and to control the uterine bleeding. It is believed that amniotomy immobilizes the portion of the placenta which is separated, which promotes local thrombosis and prevents further hemorrhage and separation. Like other organs of the body the placenta has a functional reserve. Clinical experience would indicate that a third or more of the placenta may be detached and the fetal needs be sustained. Should labor fail to occur some two to four hours after rupture of the membranes, a small amount of a pituitary preparation is administered.

Cesarean section in the group with milder separation is utilized when effective labor fails to transpire within six to twelve hours after rupture of the membranes, or when bleeding is uncontrolled by amniotomy or when judgment dictates that further separation will result in fetal death. It is rare that cesarean section is required for treatment of continued bleeding following amniotomy. The risk of infection is not increased provided the cesarean section is performed within the period mentioned above.

It must be emphasized, therefore, that, in milder forms of the condition, cesarean section is performed primarily in the interest of the infant. Even so, the fetal mortality approaches 10 per cent, for prematurity, hyaline membrane disease, and the effect of anoxia on the central nervous system all take their toll. In milder types of cases the fetal mortality in this clinic is not appreciably greater with conservative pelvic delivery. Regardless, if a cesarean section is contemplated, "a clot observation test" is performed prior to surgery to insure the adequacy of the clotting mechanism.

By contrast, the treatment of patients with the severe form of premature separation is directed entirely in the interest of the mother. The summation of the stillbirth and the neonatal morbidity and mortality from the extreme intrauterine asphyxia which is already present where severe premature separation exists attest to the futility of treatment designed primarily to salvage the baby. While one may be inclined to perform a cesarean section immediately, should the fetal heartbeat be perceptible at the time of the diagnosis of severe premature separation is made, the relative risk involved hardly justifies such a gamble. Indeed, it is a gamble to operate upon these severely ill patients without efforts first being made to combat the shock and to ascertain the status of the clotting mechanism. Rather than immediate delivery at the moment the diagnosis is established, which would mean cesarean section in nearly every instance, a more deliberate plan of treatment and study of the patient is pursued.

The first step in the management of these patients is to determine whether an afibrinogenemia exists. Blood is drawn from the antecubital vein for the "clot observation test," a procedure which is repeated hourly until the patient is delivered. Where fibrinogen concentration is decreased to a critical degree, initial clotting may be absent. *More frequently, however, clotting appears, followed within the hour by fragmentation and dissolution.* These findings demand immediate fibrinogen replacement to restore the ability of the blood to clot, a situation which cannot be corrected by multiple transfusions alone. The amount of fibrinogen administered will depend upon the clotting behavior of the blood in subsequent venous samples as seen in the "clot observation test."

Simultaneously on entrance multiple transfusions are begun to combat shock and restore blood volume to normal. Where shock and circulatory collapse are a constant threat, venous cutdowns are routine to insure uninterrupted parenteral therapy. On the average, two to four transfusions are given during the first hour. Coincidentally, where there is evidence of afibrinogenemia, an equal number of grams of fibrinogen (Cohn's Fraction I) dissolved in dextrose and water are administered intravenously. Morphine and atropine are given to quiet the patient and prepare her for an anesthetic if needed. The operating room is prepared for any eventuality.

Early in the second hour a pelvic examination is performed in the operating room to determine the condition of the cervix and to rupture the membranes. Under adequate morphine analgesia with avoidance of an anesthetic if possible, the membranes are ruptured regardless of the length and dilatation

of the cervix. While it is realized that labor will not eventuate in every instance following rupture of the membranes, effective uterine contractions often appear even when the cervix is uneffaced and barely dilated initially. The fact that productive labor may ensue even when conditions are unfavorable for induction justifies the routine rupture of the membranes before resort to cesarean section. Moreover, from the experience gained from these and other patients, the process of defibrination seems to decrease and fibrinolytic enzyme activity diminish or disappear entirely following artificial rupture of the membranes (Case 6). If this proves to be a constant response, this alone justifies the procedure.

During the third and fourth hours, additional blood and fibrinogen are administered on indication. It is anticipated that by this time the patient will have recovered fully from shock, her vital signs will be stabilized, and labor will have begun. Under these circumstances and with the clotting mechanism known to be normal, she may now face cesarean section without undue risk. Indeed, in the absence of effective labor, some four to twelve hours following artificial rupture of the membranes, cesarean section is performed. While these patients remain undelivered, recurrence of the incoagulable state of the blood is possible while a prolonged and drawn-out labor would seem unwise in a patient who has already experienced an episode of severe shock. In the belief that a skillfully given inhalation anesthetic in obstetrics is safer than a well-administered spinal anesthetic, the former is preferred for delivery. A further reason for avoiding spinal anesthesia is the ever-present hazard of impending or recurrent shock in these patients.

Discussion

Indications that a state of incoagulable blood might exist in premature separation of the placenta have appeared sporadically in the literature since 1901 when DeLee[27] first noted a hemophilia-like condition in the blood of a patient who died with uteroplacental apoplexy. In 1922 Willson[28] in a review and a report of his own experience discussed the possibility of an interference with normal blood coagulation in patients with premature separation and suggested that a circulating toxin, which he chose to call a hemorrhagin, might be involved. In 1936, Dieckmann,[29] in a study of the blood chemistry and renal function in premature separation, observed that a certain number of patients had a prolonged bleeding time and in some instances there was a marked decrease in blood fibrinogen. Moloney and his associates[19] report upon a patient with acquired afibrinogenemia in pregnancy with a pathological diagnosis of premature separation. Moloney and his colleagues were the first to include fibrinogen as an adjunct to blood transfusion in the treatment of this condition. These authors favored the concept that the hemorrhage was related to vessel damage due to toxin arising within the decidua or from a proteolytic enzyme effect.

The cause of afibrinogenemia in severe premature separation of the placenta remains speculative. It has been attributed to the entrance into the maternal circulation of a substance or substances from the uterus which in turn

defibrinates the blood. Those materials suggested which might do this include thrombin from the retroplacental clot,[16] a proteolytic enzyme from the decidua.[16, 18] and thromboplastin derived presumably from the damaged decidua and placenta.[15, 16, 18, 20, 22] The consensus of present-day evidence indicates that thromboplastin is the most likely substance responsible for the defibrination.

During the course of an investigation to determine whether the placenta had a property which might be responsible for the pathology of the syndrome complex of eclampsia, Obata[30] was impressed by the observations that following the "injection of placental extract in mice, hemorrhages and thromboses in the animals were in agreement with the anatomical features of eclampsia but the decreased coagulability of the blood appeared to be a discordant finding." Later in 1929 Sakurai[31] defibrinated animals by injection of placental extracts. Eley[32] in 1936 demonstrated an antihemophiliac activity in saline extracts of placenta and subsequently produced intravascular coagulation in the blood of guinea pigs and monkeys by lethal amounts of the material. Howell[33] in 1941 described the sequence of effects on the circulation of dogs when thromboplastin was injected. With excessive amounts death was due to extreme intravascular coagulation. Defibrination and incoagulable blood resulted when sublethal doses were administered. A negative phase was described during which further injection of thromboplastin produced no systemic effect. Chargaff[34] in 1945 identified the coagulant factor contained in saline extracts of placenta as thromboplastin protein. Schneider,[35, 36] in 1947, in a reinvestigation of Obata's experiments in mice and his own on rabbits, concluded that the agent which accounts for the toxic effects and fibrin deposition is thromboplastin. Schneider[35] further observed that following sublethal doses of placental extracts, mice were able to withstand many times the lethal dose. The period of desensitization continued for some 8 to 12 hours. This refractory phase was interpreted as due to inactivation of the placental toxin (thromboplastin) by a serum factor, an antithromboplastin. Fulton and Page[37] in 1948 in similar experiments confirmed the presence of a refractory phase in mice following the injection of a crude thromboplastic extract prepared from the placenta. These observers noted that during the time the animals were able to survive lethal doses of the preparation, the blood was incoagulable. Upon the intravenous administration of fibrinogen, the mice again became sensitive. These investigators attributed the refractory phase to a defibrinated circulation.

These findings provide the basis for the assumption that thromboplastin is the probable agent responsible for the incoagulable blood in premature separation. The coagulant presumably has its origin in the damaged tissues of the detached placenta and the neighboring decidua. The manner in which the thromboplastin escapes from the uterus must differ somewhat in the case of premature separation from that described previously for amniotic fluid infusion.[24]

With respect to premature separation of the placenta, there is a rise in intrauterine pressure when the retroplacental clot attains an appreciable size.

The gush of blood and amniotic fluid commonly seen at cesarean section when the uterus is opened in such cases attests to the fact that the intrauterine pressure is significantly increased. We herein postulate that when the intrauterine pressure exceeds the pressure within the venous sinusoids at the site of placental detachment, the coagulant-containing materials are forced into the latter blood channels as the result of the pressure difference. As long as the membranes remain intact, the intrauterine pressure is maintained and probably increases with further retroplacental bleeding. Such a concept is compatible with the observation that clotting difficulties have never been seen when a small area of the placenta is involved but only when retroplacental bleeding and the degree of concealed hemorrhage have been marked. *The arrest of defibrination which has been noted to follow artificial rupture of the membranes is submitted as further evidence that increased intrauterine pressure is responsible for the escape of coagulant material from the uterus.*

Fibrinolytic activity could be identified on occasion in the blood of these patients (Case 1).[12, 14] By definition fibrinolysis has been said to be present when the clot of whole blood or diluted plasma disappears in less than 24 hours at 37° C.[38] Such a definition, however, must assume that fibrinogen levels are sufficient for normal clot formation. Therefore, in these cases fibrinolytic activity must not be confused with *clot fragmentation, an effect which occurs when the fibrinogen concentration is below that necessary for the formation of a mechanically stable clot.* The term fibrinolysis, accordingly, should be restricted to those instances where clot dissolution occurs in the presence of proved normal fibrinogen concentrations.

Recently the possibilty of a fibrinolytic activity in these patients has been challenged by the failure to demonstrate a fibrinolysin in studies concerned with defibrination experiments in dogs.[22] Nevertheless, clot dissolution has been seen in severe cases of premature separation of the placenta following restoration of fibrinogen levels and so indicating the presence of a fibrinolysin. With normal fibrinogen levels and after rupture of the membranes, clot fragmentation disappeared. This change in clot stability under these circumstances indicates that a fibrinolysin was presumably present. Moreover, in a patient who recovered from amniotic fluid embolism with afibrinogenemia, clot fragmentation was observed after normal fibrinogen values were achieved.[39] The recent demonstration of fibrinolytic activity in a fatal case of amniotic fluid infusion or embolism with defibrination adds to the evidence that a fibrinolysin appears when thromboplastin-containing material enters the systemic circulation.[40] While the opinion has been expressed by us that the presence of an enzyme is of more than theoretical importance and has clinical significance, an erroneous impression exists that we are of the opinion that a circulating fibrinolysin is solely responsible for the resulting afibrinogenemia.[22]

Fibrinolysin or plasmin, while capable of dissolving a fibrin clot,[41, 42] according to some authorities also digests fibrinogen and prothrombin.[43] The continual utilization and conversion of fibrinogen into fibrin as a function of the normal reparative processes of the body[44] suggests that minute amounts

of fibrinolysin are required to prevent excessive fibrin deposition on the endothelium, particularly in the capillary bed. The presence of a fibrinolytic inhibitor or antiplasmin in the blood is believed to furnish a physiological antagonist which impedes excessive fibrinolytic activity.[42, 45] Regardless of these theoretical considerations as to function of fibrinolysin or plasmin in the normal physiology of the circulation, it is accepted that the enzyme is involved in the body's reaction to injury.[12, 14, 41, 42, 43]

As to the source of the enzyme, it has been shown recently[46] that fibrinolysin is present in the areas of the vascular system where the blood is in a fluid state at postmortem. This is in keeping with Virchow's significant description (1871) that the blood at autopsy is often clotted in the heart and great vessels, rarely in the limbs, and never in the capillaries. From such circumstances it has been adduced[46] that the enzyme is probably derived from the endothelial cells of the blood channels and body cavities.

At least four possibilities may be submitted to explain the presence of fibrinolytic activity in patients with severe premature separation of the placenta. First, a fibrinolytic enzyme as such may be produced and released in excessive amounts from the uterus. Second, fibrinolytic activity could be increased by injury to the endothelium as a result of intravascular clotting precipitated by the introduction of thromboplastin. This latter response is regarded as an adaptive mechanism to maintain the patency of blood channels in the face of abnormal fibrin deposition. Third, some substance presumably discharged from the uterus might depress antiplasmin or inhibitor activity and thereby enhance the effect of circulating fibrinolysin. Finally, the enzyme has been readily identified in the presence of shock.[41]

Indirect evidence that the enzyme or the provoking factor for the activation of fibrinolysin originates in the uterus is the observation here reported that the enzyme tends to disappear from the patient's blood following artificial rupture of the membranes. Fibrinolytic activity has been identified in the serum of patients with severe toxemia and it has been hypothesized[47] in the latter instance that the source of the enzyme is necrotic decidua. Fibrinolysin is demonstrable in the blood of the nonpregnant individual in the presence of abnormal fibrin deposition.[42] Reference has already been made to the presence of fibrinolytic activity in amniotic fluid infusion where intravascular clotting is believed to be extreme. In premature separation of the placenta an excessive amount of fibrinolysin would therefore be expected following injury to the capillary endothelium from the fibrin deposition associated with defibrination. It is evident that in these patients a fibrinolysis may arise from several sources. No evidence whatever can be offered regarding the presence of unusual amounts of antifibrinolytic or antiplasmin activity.

It has long been recognized that premature separation of the placenta may complicate pregnancy toxemia. Recently Schneider has submitted the hypothesis that placental separation and pregnancy toxemia are identical with respect to causation. Indeed, he states that "eclampsia may be the result of partial premature separation of the placenta." This view is based on his belief that eclampsia may be mediated by an autoinfusion of thromboplastin

and the resultant effect of "fibrin embolism," namely, intravascular coagulation with partial defibrination. Schneider[48] is of the opinion that labor will increase the degree of placental separation and produce further deposits of fibrin. He concludes that the treatment of eclampsia and fulminating preeclampsia should include the prevention of labor.

There is no doubt that when a careful morphologic search is made, fibrin deposition is seen in the organs of patients who die from eclampsia. However, the distribution through the body and degree of fibrin deposition are extremely variable. Whether these deposits of fibrin represent some degree of intravascular clotting or are the result of local vessel reaction to an intoxicant remains to be elucidated.[49] Fibrin deposition is seen in other conditions such as those involving sepsis and in hypertensive states.

We are reminded that some 50 to 75 per cent of patients with abruptio placentae do not have hypertension and proteinuria. However, when patients with premature separation of the placenta exhibit proteinuria, the finding is not necessarily indicative of an associated pregnancy toxemia. Concealed hemorrhage, regardless of etiology, has been indicated as a cause of proteinuria.[50]

On a morphologic basis, premature separation of the placenta either grossly or microscopically has been reported to occur with greater frequency in the more severe forms of pregnancy toxemia.[26] These findings have been interpreted to mean that premature separation is a manifestation rather than a cause of pregnancy toxemia.[26, 49] As part of the generalized vasospasm of the toxemia, constriction of the uteroplacental spiral vessels is believed to result in decidual necrosis and subsequent premature separation.

Regardless of the increased frequency, any direct relationship between the degree of premature separation and the severity of the toxemia remains controversial and unproved. From a clinical standpoint in this series of patients with severe premature separation, no parallelism with either the presence or the extent of the toxemia could be clearly established. Some of the most troubling patients were apparently free of toxemia while others developed the separation between the twenty-fifth and thirtieth weeks of pregnancy, a period not commonly associated with pregnancy toxemia.

With respect to the problem of incoagulable blood as related to preeclampsia and eclampsia, a hemorrhagic diathesis is rare indeed in patients with pregnancy toxemia. While Dieckmann[29] records such an occurrence in eclampsia, he emphasizes that fibrinogen values in this disease are above those for normal pregnancy. Blood fibrinogen determinations in over one hundred patients with varying degrees of pregnancy toxemia during this study confirm these findings. It is hardly conceivable that in eclampsia and in the absence of severe premature separation the amount of fibrin deposited is great enough to reduce the circulating fibrinogen to a hemorrhagic level. In the event fibrinogen concentration is reduced to a critical level in eclampsia, it could be due to either a decreased production by a damaged liver[51] or excessive utilization of the protein as the result of coexistent severe premature

separation. In the former instance prothrombin as well as fibrinogen would be significantly decreased in the peripheral blood, a finding which would prove important in differentiating the cause of the bleeding tendency.

Eastman[52] is of the opinion that eclampsia and premature separation of the placenta should not be placed in the same category with regard to obstetrical management. This view is shared by us. If the theoretically deleterious effects of labor are to be avoided, cesarean section would be routinely required for patients with severe premature separation of the placenta and eclampsia. The indiscriminate use of such a surgical procedure in these often desperately ill patients would undoubtedly prove disastrous.

Recent reviews indicate that immediate cesarean section, however, still remains the method of choice for the delivery of patients with severe premature separation of the placenta,[53] but for reasons other than those previously considered. The recommendation for early surgical treatment is based on the belief that the uterus with Couvelaire changes is often subject to ineffectual labor and postpartum atony. It is argued that cesarean section will eliminate death from hemorrhage by the prompt termination of pregnancy and at the same time allow the operator to perform an immediate hysterectomy in the event uncontrolled postpartum hemorrhage should ensue. The concept that the uterus in these cases will not contract sufficiently to deliver the fetus or to effect adequate hemostasis following delivery is at variance with clinical experience. What in practice is the most impressive is the fact that even when Couvelaire changes are marked the quality of uterine contractions are many times sufficient to allow pelvic delivery. Further, postpartum hemorrhage rarely supervenes following pelvic delivery and we now have a reason to suspect that when it does occur it may be due to a clotting defect (Case 3). The majority of these patients therefore can be delivered per vaginam if they are only afforded an opportunity. Labor will not be productive in every instance, however, and cesarean section will be required for reasons already mentioned.

Hysterectomy as the preferred method of treatment of postpartum hemorrhage associated with premature separation is in our opinion "placing the cart before the horse." Hysterectomy transfers the bleeding tendency to areas outside the uterine corpus, namely, the ovarian pedicle, cervical stump, and incised visceral and parietal peritoneum. Oozing or active bleeding from these areas irrespective of ligature is a commonplace experience when hysterectomy is performed solely for the control of bleeding in severe premature separation of the placenta.

We believe that in most cases of intractable postpartum hemorrhage with abruptio a defect in the clotting ability of the blood is responsible, rather than uterine atony. It is proposed that the correction of this deficiency in blood coagulation will remove hysterectomy from its place as the method of choice for the treatment of postpartum hemorrhage associated with premature separation of the placenta.

The idea has been put forth that the clotting mechanism will deteriorate if the patient remains undelivered, and that an immediate cesarean section should be performed to obviate such a happening. This reasoning disre-

gards the significant fact that the clotting mechanism may already be deficient when the patient is first observed. *The optimum treatment must take into account the fact that the patient's blood is or is about to become incoagulable.* We now know that deterioration in the clotting mechanism may be arrested by rupture of the membranes. Finally, if a deficiency does develop in the clinical course of a patient with premature separation of the placenta, it is now possible to restore the normal clotting ability of the blood by definitive therapy prior to labor and delivery (Case 2).

It must be emphasized that multiple transfusions alone will not raise the circulating fibrinogen to effective coagulant levels in the severely defibrinated patient. Actually a single transfusion cannot increase the blood fibrinogen concentration more than 5 to 10 mg. per cent in these patients when they are bleeding actively. Several patients included in this series received 5,000 to 8,000 c.c. of blood and yet continued to bleed in the presence of clot fragmentation. The situation was corrected by subsequent fibrinogen infusion.

The dangers of homologous serum jaundice must be considered whenever blood, plasma, or blood fractions are administered. The fibrinogen used in this series was sterilized mainly with nitrogen mustard and in a few instances with ultraviolet rays. Jaundice was not seen in the patients treated in this series. It is concluded that the fear of homologous serum jaundice should not prevent the use of fibrinogen when it is needed. Therefore, it is recommended that 10 Gm. of fibrinogen, sufficient to treat one patient adequately, should be available in every hospital practicing obstetrics.

Summary and Conclusions

The management of premature separation of the placenta continues to differ from clinic to clinic and this fact alone indicates that no one form of treatment is entirely acceptable. The majority of patients who die from this complication do so from immediate and extensive blood loss while the remaining deaths usually follow renal and pituitary damage. Evidence is accumulating that the hemorrhagic deaths result from a defect in the clotting mechanism. The fundamental disturbance is a reduction in the circulating fibrinogen into a hemorrhagic range. Fibrinogen depletion is believed to result from extensive intravascular coagulation of blood. This is initiated presumably by the introduction into the systemic circulation of a thromboplastic material derived from uterine contents. The afibrinogenemia has been observed only in the most extensive form of premature separation. Any alteration in the hemostatic mechanism is believed to follow rather than to precede or initiate the placental separation. Furthermore, once the patient is safely delivered, the coagulation components do not decline further, a fact that emphasizes the transient nature of the hemostatic disturbance.

While prothrombin and its accelerators may become altered by the catastrophic upset in the coagulation mechanism here encountered, it appears unlikely that these clotting elements are reduced sufficiently to cause the blood to become incoagulable. Such a belief is warranted unless it can be demonstrated that the addition of fibrinogen to the incoagulable blood in vitro fails to

produce a clot. Where the clot exhibits instability in the "clot observation test," such an occurrence is believed due primarily to inadequate fibrinogen concentration or the presence of a fibrinolytic enzyme or both.

On the basis that a state of incoagulable blood often exists in patients with severe premature separation of the placenta, we have contested the advisability of immediate cesarean section. Further, the place of hysterectomy in the control of postpartum bleeding in these patients has been questioned. It is suggested that in the majority of instances the cause of the postpartum hemorrhage is afibrinogenemia, the correction of which will obviate the need for removal of the uterus.

It has been recommended that a more deliberate plan of obstetrical action be taken in the case of patients with severe premature separation of the placenta. The treatment herein outlined is concerned with the detection of patients with incoagulable blood. Failure of the blood to clot initially or fragmenting of the clot or dissolution of the clot in the clot observation test within an hour after the blood is drawn indicates ineffective hemostasis due to afibrinogenemia. In the face of such findings, fibrinogen therapy is mandatory to restore the clotting mechanism. Otherwise it will be impossible to maintain an effective blood volume with multiple transfusions alone.

Artificial rupture of the membranes is believed to be an important part of the treatment directed toward promoting labor, and preventing further fibrinogen depletion and the appearance of a circulating fibrinolysin.

After the initial shock has been eliminated and the clotting mechanisms restored to normal, abdominal hysterotomy is considered in the absence of effective labor. Cesarean section under these favorable circumstances seems preferable to an unpredictable and possibly exhausting labor in a patient recently recovered from shock.

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III. MATERNAL AFIBRINOGENEMIA ASSOCIATED WITH LONG-STANDING INTRAUTERINE FETAL DEATH*

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IN THE course of an investigation of the clotting mechanism in normal and abnormal pregnancy, three patients were encountered who had dead babies in utero and bled alarmingly at delivery.[1] In each instance the fetus had been retained in utero for many weeks after death. These patients were by chance all Rh negative and fetal death had resulted from blood incompatibility. No special significance was attached to the fact that the patients were Rh negative but to the fact that labor was delayed for several weeks following fetal death.

A study of the blood of these patients revealed a striking depletion of fibrinogen and some reduction of prothrombin activity, although the latter never reached hemorrhagic levels. Despite a search fibrinolytic activity could not be demonstrated. On the basis of normal liver function tests in one patient studied, it was concluded that the lack of fibrinogen was not the result of failure of production of the plasma protein. The suggestion was made[1] that diminished fibrinogen concentration was due to the possibility that "thromboplastic material from the uterine contents gains entrance into the maternal circulation and causes intravascular coagulation with consumption of fibrinogen." Afibrinogenemia was never detected where death in utero had been of relatively short duration, suggesting that a marked degree of autolysis of decidual and placental tissue was a prerequisite to the production of the syndrome.

One patient developed afibrinogenemia prior to labor, while the others were about to enter or were in active labor when this alteration in the coagulation mechanism was noted. Neither clinical nor pathological evidence of a premature separation of the placenta was evident in these patients. The idea was offered that the myometrial contractions acting on the uterus in a sponge-like manner expressed coagulant material from the macerated uterine contents into the maternal circulation.

The circumstance under which the clotting mechanism became deficient warranted placing these patients in a separate group with respect to the syndrome of acquired afibrinogenemia in pregnancy. Specifically, here were patients who developed an afibrinogenemia in the absence of premature separation of the placenta. This is an important difference to recognize, else the clinical significance of longstanding death in utero will not be fully appreciated with respect to early diagnosis and treatment. It must be emphasized that the outstanding clinical feature in these patients is that the hemorrhagic

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tendency may first become manifest by ecchymoses and bleeding from the mucous membranes of the respiratory and gastrointestinal tract.

Since our earlier report[1] we have been involved indirectly in the treatment of other similar patients who were given fibrinogen supplied through the facilities of the Boston Lying-in Hospital and the Blood Grouping Laboratory of the Children's Medical Center of Boston. One of the cases now included (Case 4) has been previously reported in a detailed and complete account[2] and only the more important features of the clinical course will be considered here.

CASE 1.—Mrs. N. W., No. 1239, a 37-year-old para i, gravida ii, entered the hospital in the thirty-sixth week of her pregnancy, some five weeks after her baby had succumbed in utero. Her previous pregnancy was normal. The patient was type O, Rh positive and her husband was type B, Rh positive. After a labor of 10 hours' duration, the patient delivered spontaneously a macerated stillborn infant. The placenta was expressed 5 minutes later. Ten minutes after delivery excessive bleeding was noted, although the uterus was well contracted. The patient's blood was incoagulable in a clot observation test at this time. Under ether anesthesia the uterus, cervix, and vagina were found to be intact. The uterus and vagina were packed with Hemopack and transfusions were started. Irrespective of multiple transfusions totaling 4,000 c.c. of fresh blood, vaginal bleeding continued and the patient appeared to be losing ground. Accordingly, 4 hours after delivery, a subtotal hysterectomy was done. The cervical stump, the abdominal wall, and all surfaces oozed constantly at operation. Even a finger prick bled so profusely that a pressure dressing was necessary. The clot observation test produced little or no clot. There was very little precipitation of fibrinogen when the patient's plasma was heated to 56° C. for 30 minutes. The platelet count and prothrombin time were normal, and because of these findings a diagnosis of afibrinogenemia was made. In spite of continuous transfusions the patient's condition remained critical and she continued bleeding through her abdominal dressing. Six hours after hysterectomy, 2.5 Gm. of fibrinogen was infused intravenously. Thereafter, there was a sudden cessation of bleeding. The patient improved satisfactorily and she was discharged on the seventh postoperative day.

CASE 2.—Mrs. A. M., No. 1240, a 26-year-old para i, gravida iii, entered the hospital in the thirty-first week of pregnancy with vaginal bleeding. The patient was Rh negative. Her first pregnancy was uneventful. The second pregnancy terminated in a stillbirth associated with a high maternal anti-Rh titer. The present gestation was normal until 22 weeks, although the anti-Rh titer was 1:128. In the twenty-third week fetal movements disappeared and the fetal heart beat was no longer heard. Thereafter the uterus became smaller and the patient had several episodes of brownish vaginal discharge.

After a labor of 2 hours' duration, the patient was delivered of a severely macerated fetus with membranes and placenta intact. A profuse vaginal hemorrhage ensued. Afibrinogenemia was diagnosed since the clot observation test formed a very small soft clot. Excessive bleeding continued in spite of a firm uterus and transfusions. Two and one-half Gm. of fibrinogen was infused with prompt and dramatic cessation of bleeding. The clot observation test now formed a large stable clot and the patient's subsequent course was normal.

CASE 3.—Mrs. D., No. 1241, a para 0, gravida ii, entered the hospital in approximately the thirtieth week of pregnancy. Her blood group was B, Rh positive. Her husband was Group O, Rh positive, and probably heterozygous. Extensive blood studies were done at the Blood Grouping Laboratory of the Children's Medical Center and no evidence of A-B-O incompatibility was found. Her first pregnancy had terminated in an early miscarriage. The present gestation developed normally and in the fifth month the fetal heart was heard. During the sixth month the fetal heart sounds disappeared and the uterus ceased to enlarge. Six weeks later the patient delivered precipitously at home a macerated fetus and placenta and

was admitted to the hospital because of persistent bleeding. There were no lacerations of the vagina and the uterus was well contracted. Nevertheless, severe blood loss continued. A sample of venous blood was drawn and although a clot formed it was ragged and friable and within one hour had liquefied. The quantitative fibrinogen was 88 mg. per cent and the prothrombin time 22 seconds. Two and one-half Gm. of fibrinogen was given intravenously. About 15 minutes after fibrinogen injection there was a cessation of bleeding and the patient was normal thereafter. The quantitative fibrinogen concentration after fibrinogen therapy was 150 mg. per cent and a good clot was formed in the clot observation test.

CASE 4.—Mrs. S., No. 1242, was a para iii, gravida iv. Her blood was Rh negative. The present pregnancy developed normally until the sixth month at which time the fetal heartbeat was no longer heard and the uterus failed to enlarge. The anti-Rh titer fluctuated between 1:16 and 1:64. Previous pregnancies had been normal. However, with her last delivery an adherent placenta was encountered, and blood loss was sufficient to demand a transfusion. The blood given was Rh positive from which she apparently became sensitized.

During the eighth month of the present pregnancy, and about 8 weeks after fetal death in utero, the patient awoke one morning with her mouth full of blood. Shortly thereafter ecchymoses appeared on the ankles, shins, knees, hips, wrists, and elbows. The patient was hospitalized and complete and repeated hematological studies were performed over the next four weeks. These were normal except for a low fibrinogen concentration of 91 mg. per cent. An anticoagulant could not be demonstrated and conversion of fibrinogen to fibrin was unimpaired. Prothrombin activity was 72 per cent of normal. Several attempts to demonstrate a proteolytic enzyme were unsuccessful. Administered fibrinogen was quickly utilized or removed from the plasma. Total serum proteins and plasma ascorbic acid determinations were normal. Icterus index, cephalin-cholesterol flocculation, and thymol turbidity tests were normal.

The fibrinogen concentration fluctuated between 95 and 100 mg. per cent during the period of hospitalization. Finally, two weeks beyond her expected date of confinement and twelve weeks after the fetal heartbeat was lost, a supracervical hysterectomy was performed. Prior to and during surgery 5 Gm. of fibrinogen was infused and no difficulty with hemostasis was encountered. Immediately postoperatively the fibrinogen concentration was 208 mg. per cent although for many weeks hypofibrinogenemia had existed. The specimen of the uterus revealed a complete placenta accreta associated with marked tissue necrosis. The patient's subsequent course was normal and her blood fibrinogen concentration remained at normal levels thereafter.

CASE 5.—Mrs. R. T., No. 1243, a 23-year-old para iii, gravida iv, entered the hospital in early labor in her fourth pregnancy. The patient was group O, Rh negative. Her first and second pregnancies were normal. The third pregnancy was complicated by an anti-Rh titer of 1:256. She delivered an erythroblastotic term infant who did well after transfusions.

During the present pregnancy the prenatal examination was normal at the fifth-month visit. The size of the uterus was consistent with her dates and the fetal heartbeat was heard. At her seventh-month visit the patient stated that she had not felt fetal motion for a week. The uterus had not grown beyond 5 months' size and the fetal heartbeat was now absent. A sample of blood was taken that day which clotted immediately. The clot remained well-formed with normal retraction. Blood was drawn at four-day intervals thereafter and on each occasion showed normal clot formation.

The patient was admitted to the hospital after 31 weeks' gestation in beginning labor and with a slight amount of vaginal show. Maternal venous blood was drawn at this time and showed a normal clotting time, but *within one-half hour after the blood had been secured it was again fluid.* Also within the half-hour the patient passed more than 500 c.c. of fluid blood in a sudden gush, and showed signs of beginning shock.

Compatible type O, Rh-negative bank blood was immediately administered while fresh blood was being secured from a donor. One hour after the onset of labor, the patient passed an intact placenta and sac; the fetus was macerated, and weighed only 6 ounces. There was no evidence of premature separation. Her bleeding persisted in spite of oxytocic drugs and the blood which was passed vaginally failed to clot.

The patient was supported with three 500 c.c. transfusions of type O, Rh-negative blood and intravenous saline for the next few hours while fibrinogen was secured. During this period the patient was in peripheral vascular collapse with a blood pressure of 70 to 80/40. It was remarked that on application of a tourniquet all the previous skin punctures bled noticeably.

When 2.5 Gm. of fibrinogen was infused rapidly over a 15 minute period, there was less bleeding and a definite improvement was noted in the blood pressure. As soon as 2.5 Gm. more fibrinogen was administered the vaginal bleeding ceased. A sample of venous blood produced a stable clot. From that time the patient had no difficulty and was discharged on the fifth postnatal day.

CASE 6.—No. 1244, a 28-year-old para i, gravida iv, entered the hospital for the second time in the thirtieth week of pregnancy. Her blood was Rh negative. Her first child was delivered by cesarean section for uterine inertia. Her second pregnancy was an ectopic implantation in the right tube. At the time of operation she received a transfusion from her husband who was Rh positive. Her third pregnancy terminated in vaginal delivery of a macerated full-term stillborn infant.

The patient was first seen when she was in the twenty-second week of her present pregnancy. Her prenatal examination was normal and the size of the uterus was consistent with her dates. Two weeks later the patient reported loss of fetal movements; when she was examined the fetal heart sounds were absent. The anti-Rh titer was reported as 1:1,024.

Four weeks later at the twenty-ninth week of pregnancy she was admitted for study. The clotting time of venous blood was 3 minutes, and the clot was stable. The prothrombin time was 100 per cent of normal and the blood pressure 96/62. The urine was free of albumin. She was discharged in good condition after three days of hospitalization.

During the thirtieth week the patient first noted swelling of the extremities, headaches, and one episode of hemoptysis. She was readmitted to the hospital because of rapid weight gain, hypertension of 150/86, a trace of albumin in the urine, and slight edema of the extremities. The uterus was the size of a 6 months' pregnancy and the cervix long, thick, and closed. Three samples of blood were drawn and showed prompt clot formation. However, these clots were small and disintegrated after one hour of incubation. The bleeding time was 8 minutes, the prothrombin time 25 per cent of normal, the platelets 126,000, and the tourniquet test was positive. The plasma fibrinogen level was 50 mg. per cent and no fibrinolytic activity could be demonstrated.

On the third day of this second hospital admission, the patient first noted a small amount of vaginal bleeding. She also developed large hematomas about the sites of needle punctures. Because labor did not ensue, it was decided to terminate pregnancy by cesarean section in view of (1) closed cervix, (2) pre-eclampsia, (3) a previous cesarean section.

At 9:00 P.M. 1 Gm. of fibrinogen was infused and a similar amount was given at 10:00 P.M. Venous blood drawn at 11:00 P.M. showed complete clotting within three minutes but at the end of one hour's incubation at 37° C. fragmentation of the clot was noted. At 1:00 A.M. of the following day a third Gm. of fibrinogen was administered. At 1:15 A.M. 500 c.c. of fresh blood was given. At 1:20 A.M. a classical cesarean section was carried out under cyclopropane-ether anesthesia without difficulty. A macerated, 800 gram stillborn infant was delivered. *There was no evidence of placental separation.* Surprisingly little bleeding occurred during the operation. The blood pressure shortly after the operation was 118/68. At the close of the operation, the anesthetist noticed that the patient's respirations were labored and that blood was present in the nostrils and mouth. Likewise about 600 c.c. of clotted blood on the operating table which evidently represented the bleeding that had occurred from the vagina during the operation. At 2:30 A.M. the fourth Gm. of fibrinogen was given together with another 500 c.c. of fresh blood. At 3:30 A.M. when the patient was apparently recovering from the anesthetic she stopped breathing, became cyanotic, and the blood pressure was unobtainable. Intratracheal intubation was done and a moderate amount of blood aspirated

from the respiratory tract. Continuous oxygen was started and an additional 1,000 c.c. of fresh blood was given during the next hour. The blood pressure rose to 90/60 with this treatment. However, the respirations remained irregular and stopped completely one hour after the first period of apnea and the patient died.

Gross autopsy findings six hours after death showed pulmonary edema and hemorrhage. There were also perineal hemorrhages and approximately 150 c.c. of blood was in the uterine cavity. There was no evidence of cerebral hemorrhage nor was there free blood in the bladder, intestines, or abdominal cavity.

Distance prohibited the sending of blood samples to the Boston Lying-in Hospital. We are indebted to Dr. Paul Bruns of the University of Colorado Medical School for his protocol and excellent observation and critical analysis of this case. The following verbatum report of Dr. Bruns expresses clearly the problems which these patients present.

"This case represents a maternal death due to shock and hemorrhage. The cause of this is based primarily upon fibrinopenia. This abnormality of the blood-clotting mechanism was associated with an intrauterine fetal death in an Rh-negative sensitized mother who had pre-eclampsia. This patient's death was considered preventable on the basis of the following factors: (1) inadequate correction of the fibrinopenia; (2) a poorly chosen time and method of delivery; (3) an unwise choice of anesthesia.

"Although this patient was given 3 Gm. of fibrinogen and approximately 700 c.c. of blood prior to section, in the light of subsequent events, this was considered inadequate.

"Because a limited amount (6 Gm.) of fibrinogen was on hand, it was believed that pregnancy should be terminated as soon as the coagulation defect was corrected, and, as actually happened, the added trauma of cesarean section and cyclopropane anesthesia were considered sufficient to initiate this tragic sequence of events. Although this patient's death may be ascribed to an error in obstetrical judgment, there are several aspects which deserve favorable comment:

"1. The possibility of the development of a coagulation defect was recognized in this patient early in her prenatal course and she was carefully checked at each visit for evidence of clotting abnormality. She was admitted to the hospital for study on one occasion and found to be normal and discharged.

"2. Her Rh and antibody status were carefully followed throughout her prenatal course.

"3. Adequate amounts of whole fresh Group O negative blood were kept available at all times.

"4. Six Gm. of fibrinogen were kept in readiness. The future management of such patients should include correction of the coagulation defect by adequately controlled laboratory methods. It is not believed that the size and stability of the blood clot are adequate or satisfactory as a test in circumstances other than emergencies."

Comment

Acquired afibrinogenemia in pregnancy with a resultant hemorrhagic diathesis may be seen in at least three circumstances. These include amniotic fluid infusion (embolism),[3] severe premature separation of the placenta,[4] and long-standing retention of a dead fetus in utero. With respect to the latter condition, while blood incompatibility would account for the majority of fetal deaths, it is not considered the cause of the afibrinogenemia. In this series the Rh factor was not involved in Case 3.

The significant hematological change which occurs in these patients is a defibrination of the blood. While it is true that prothrombin time in the one-stage test is occasionally observed to be prolonged, this is unduly magnified by a delay in clotting occasioned by coexisting afibrinogenemia. However,

alterations in prothrombic activity did not reach a hemorrhagic range. Changes in substances which accelerate prothrombin conversion, including antihemophiliac globulin, A-globulin, and serum prothrombin conversion accelerator (SPCA) may occupy a secondary role. However, the presence of a normal prothrombin time rules out changes in the activity of these enzymes of physiological significance.

In each of the situations mentioned, present evidence favors the belief that afibrinogenemia is the result of increased utilization or destruction rather than a diminution in production. Fibrinogen depletion is assumed to be the result of intravascular coagulation caused by the escape of a coagulant, possibly thromboplastin, from the uterus into the maternal circulation. The defibrinating material is supposedly derived from autolysis of decidua or placental tissue.

The way in which the coagulant is forced out of the uterus and into the maternal circulation differs somewhat in the three categories of patients. In this particular group of patients, it is hypothesized that the coagulant enters the maternal circulation under the impetus of uterine contractions whether they are of Braxton-Hicks type or those of true labor. Case 4 illustrates an unusual obstetrical situation which furnishes evidence for the validity of such an assumption. In this instance the patient had a complete placenta accreta so that the necrotic tissue was in direct contact with the underlying sinusoids. Marked defibrination occurred in a situation where premature separation was an impossibility.

Placental autolysis following fetal death in utero varies greatly. In many instances there is little morphological change while on occasion the placenta becomes devitalized to the point of liquefaction. It is this latter circumstance which is probably required before an afibrinogenemia will develop. Direct evidence of such marked placental changes is not apparent until delivery. Therefore, an acquired afibrinogenemia is a potential hazard for any patient whose baby had been retained for several weeks following death in utero. These patients deserve careful observation and periodic examination of the blood by the clot observation test until delivery has been accomplished. It must be emphasized that *defibrination may develop, therefore, in the intervening weeks prior to labor.*

Whenever alterations in the clotting mechanism are encountered or hemorrhagic manifestations appear, the patient should be hospitalized. Spontaneous restoration of blood fibrinogen concentration presumably will not occur while the patient remains undelivered.

The choice of obstetrical procedure to be followed must take into account that long-standing fetal death may be accompanied by intrauterine infection while any attempt to induce labor may precipitate serious uterine hemorrhage. Normal labor and pelvic delivery would appear to be the safer and preferred method of treatment in these patients whose hemostatic mechanism is disturbed. Whenever possible an obstetrical policy of expectancy should be pursued and the spontaneous onset of labor awaited. During the interim blood transfusions may be required to correct any anemia.

In certain instances, however, the hemorrhagic effects may reach such proportions that termination of the pregnancy becomes mandatory. Reference has been made to the possible dangers of induction of labor. In rare instances, therefore, recourse to abdominal delivery must be made. To avoid peritoneal contamination where intrauterine infection is likely, supracervical hysterectomy rapidly performed would seem the wiser and safer procedure.

Fibrinogen levels must be restored sufficiently to cause stable clot formation at the time of onset of spontaneous labor or before embarking on any operative procedure. The administration of fibrinogen prior to this time is of little avail in restoring the normal blood levels since this substance continues to disappear from the blood under these circumstances until delivery has been effected.[2] The predelivery blood concentration of fibrinogen, moreover, will be raised only temporarily by the administration of Fraction I.

During the time of labor or any operative procedure, the circulating blood volume should be maintained by transfusions, preferably of fresh blood to insure adequate amounts of accelerator substances. If fibrinogen levels are maintained, intrapartum and postpartum hemorrhage are not anticipated. Moreover, afibrinogenemia will not recur following delivery.

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THE PATHOLOGIC ANATOMY OF ECLAMPSIA, BILATERAL RENAL CORTICAL NECROSIS, PITUITARY NECROSIS, AND OTHER ACUTE FATAL COMPLICATIONS OF PREGNANCY, AND ITS POSSIBLE RELATIONSHIP TO THE GENERALIZED SHWARTZMAN PHENOMENON

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UNTIL the present, eclampsia, bilateral renal cortical necrosis with premature separation of the placenta, and pituitary necrosis incident to pregnancy have been regarded as more or less distinct, separate clinical and pathologic entities. While indeed they do present clinical and pathologic differences, some of the pathologic findings in these cases suggest a common etiological background.

It is the purpose of this report to describe the pathology of cases at the Boston Lying-in Hospital belonging to these three categories, to point out the similarities between them, and to propose an explanation, based on animal experiments, of the basic pathologic-physiologic process which is at fault. Briefly, it is suggested that the disturbance leading to the pathologic changes of eclampsia, premature separation with renal cortical necrosis, and pituitary necrosis is essentially a sudden intravascular deposition of fibrin which is caused by a mechanism similar to, if not identical with, the generalized Shwartzman phenomenon in experimental animals.

While this report does not constitute a review of the literature, for the purposes of clarity and completeness a summary of the classic description of the pathologic changes in the three syndromes will be presented.

Eclampsia

According to Dieckmann[3] there are usually varying degrees of edema of the legs, and not infrequently a generalized edema. Areas of hemorrhage into and beneath the skin and about needle puncture marks occur with some frequency. The fluid in the peritoneal, pleural, and pericardial cavities is almost always increased in amount.

In general, the pathologic findings in eclampsia are hemorrhage and necrosis, for the most part involving the liver and the brain, and, less constantly, other organs. The liver does not exceed normal size; it is firm and usually somewhat pale. The surface may be covered with scattered red, irregular patches, due to subcapsular hemorrhages. These can often be seen on the cut

surface. There is a predilection for the hemorrhage to be limited to, or most marked in, the right lobe. Occasionally, yellow or white patches of ischemic infarction may be seen.

Microscopically, the lesions begin about a portal space but may extend toward the center of the lobule. They may be confluent, and consist essentially of dilation of the sinusoids, with hemorrhage, necrosis of surrounding liver cells, polymorphonuclear leukocytic infiltration, and often fibrin deposition in the sinusoids. The lesions may be very numerous or so few that several slides must be examined to find a single example.

According to Sheehan[15] these lesions are related to the mortality of eclampsia since they are found in nearly all patients who die of this condition, but in only one-fourth of those patients who survive their eclampsia and die of other causes in the puerperium. Dieckmann is of the opinion that the primary lesion is a marked dilation or ectasia of the capillaries about the portal space. Teacher[21] believed that the necrosis of the liver cells occurred first and was followed by hemorrhage. Schmorl[13] stressed the significance of the extensive thrombosis found in the smallest vessels in the periportal connective tissue and believed they were the cause of the necrosis. Ingerslev and Teilum[9] concur in this opinion. Schmorl reported periportal hemorrhage and necrosis in 71 of 73 livers from patients with eclampsia.

The kidneys are usually normal in size. They may be dark red with indistinct corticomedullary differentiation or they may be pale gray-white. On section the cortices are pale and small hemorrhages may be seen.

Microscopically the capsular space contains a granular protein precipitate. Red blood cells may be seen in the tubular lumen. Stasis of the blood in capillaries, venules, and arterioles can be demonstrated and thrombosis is not infrequently seen. Some authors describe thickening of the basement membrane of the glomerular capillaries, while others, Canny[2] and Sheehan,[15] question its existence.

The lungs usually show varying degrees of edema and congestion, and early bronchopneumonia is not uncommon.

Petechial hemorrhages in the heart and areas of focal necrosis in the myocardium are found in 40 to 60 per cent of the cases. The adrenals and other organs may show capillary hemorrhages and thromboses.

The brain may show evidence of edema. Sheehan[15] reports macroscopic hemorrhages, softening, or meningeal hemorrhage in 35 per cent of patients with true eclampsia and in 45 per cent of those with pre-eclampsia who had coma with no convulsions or with only one convulsion.

Kellogg[10] reported cornual and subserosal hemorrhages of the uterus in over half the cases. These are usually associated with, and are more marked in, abruptio placentae.

Bilateral Cortical Necrosis of the Kidneys

Bilateral cortical necrosis and symmetrical cortical necrosis of the kidneys are terms used to indicate a pathologic entity of obscure etiology characterized by more or less complete and uniform necrosis of the cortex of both kidneys,

including the columns of Bertin. Duff and Murray[4] in 1941 collected 71 cases of this disease from the literature and summarized the pathologic and clinical findings.

In the majority of cases, the important changes are confined to the kidneys which are slightly enlarged, swollen, and soft. The capsule strips with ease leaving a perfectly smooth surface. Although there are differences in detail from case to case the lesions in all instances are of the same general character, representing ischemic necrosis of the renal cortex of varying degrees of severity. Some show multiple small infarcts through the cortices with large amounts of uninvolved cortical tissue, while others have multiple closely set infarcts. Many show complete confluent necrosis of almost the entire cortex.

These differences do not represent stages in a chronologic sequence but rather differences in the extent of necrosis from case to case. In general the more extensive the necrosis the shorter the survival time after onset. The kidney surface appears mottled red and yellow, or the entire surface is tawny yellow with red flecks. The medulla is usually free of necrosis. The grossly visible renal arteries and veins are free from occlusion of any form in almost every case with few exceptions.

The early red lesions are correspondingly hemorrhagic under the microscope, while older lesions, grossly yellow, prove to be composed of almost bloodless necrotic tissue. The older areas of necrosis are bordered by a hyperemic and hemorrhagic zone corresponding with the red line in the gross specimens at the margin of the yellow patches.

The glomeruli of the infarcted tissue are normal in size but necrotic. Occasionally fibrin thrombi have been seen in the glomerular capillaries. The tubules are necrotic showing all degrees of nuclear degeneration up to complete disappearance of nuclear staining. Glomerular capillaries and other vessels at the periphery of infarcted areas are distended with red blood cells and in those regions there are numerous polymorphonuclear leukocytes but no bacteria.

Some, but not all, authors have described necrosis of arterial walls, especially those of the interlobular arteries or vessels of 150 microns or less in diameter. Regardless of whether primary arterial necrosis was present or not, there was found in almost every case some form of plugging of intralobular arteries or their branches. The exact character of the intravascular masses is a point upon which there is considerable difference of opinion. Some authors state that they are thrombi, fibrin thrombi or hyaline thrombi, without describing their appearance in any detail. In some instances, the thrombi are described as being composed of platelets and a fibrin meshwork with red and white blood cells, or consisting merely of an eosinophilic homogeneous mass. Some thrombi appeared compact in their peripheral layers next to the arterial wall but were delicate or even patent toward the center. These thrombi may be formed in the afferent arterioles of the glomeruli and even in the glomerular capillaries. In one case not only glomerular capillaries but efferent vessels

contained the thrombi. In general the thrombi show no evidence of organization except in a few instances when they occurred in vessels proximal to the infarcted areas.

No changes in organs other than the kidneys are found constantly in association with bilateral renal cortical necrosis. However, 3 cases with lesions resembling eclamptic necrosis of the liver; 1 case with multiple hemorrhagic ulcerations of the large intestine with "hyaline necrosis" of the underlying blood vessels; 4 cases with multiple small infarctlike areas of recent necrosis in the spleen with thrombosis of neighboring arterioles; 4 cases with multiple small areas of hemorrhagic necrosis of the adrenals; and 3 cases of numerous petechial hemorrhages in the brain have been described.

The clinical background of the 71 cases was somewhat varied; however, the majority, i.e., 48 cases, were associated with pregnancy. The ages of these patients are distributed throughout almost the whole childbearing period, but almost two-thirds occurred in women over 30 years of age and one-third in women 30 to 35. The number of previous pregnancies varied from zero to fifteen. The pregnancies were terminated with striking frequency by premature delivery and/or stillbirth in all but one case. Gestation was terminated usually in the fifth to eighth month. Twenty-one had premature separation of the placenta and 8 had pre-eclamptic toxemia. Convulsions occurred in 12 cases before the beginning of anuria. Cesarean section was performed in 4 cases, a Credé removal of the placenta in 1, and the membranes were artificially ruptured in 6 with the development of shock in 1. Postpartum infection of the uterus occurred in 6 cases. In all cases of infection, anuria preceded the evidence of infection. Out of the 45 cases, the onset of anuria began on the day of delivery in 36, preceded delivery in 4, and was within 3 days post partum in 5.

Among the 23 cases unassociated with pregnancy, 15 of which patients were males, there was a wide variety of suggested causal factors. Infections, such as scarlet fever, diphtheria, tonsillitis, pneumonia, pneumonia with camphor injections, tuberculosis, therapeutic malarial infection, and dysentery were noted. Absorption of chemical toxins was noted in 8 cases. Camphor, alcohol, almond extract, cobra venom, and thyroid extract were among these. In 3 cases no antecedent event of possible causal significance was mentioned.

Regardless of the clinical background, the subsequent clinical course of bilateral cortical necrosis cases was essentially the same and was practically that which follows extirpation of the kidney. Anuria or extreme oliguria marked the onset of the disease. This was accompanied by pain or tenderness in the loin or epigastrium or radiating along the course of the ureter. The anuria may persist or the patient may put out a very small volume of urine. Death occurred in this group of patients between 2 and 32 days after the onset but was most common 4 to 12 days later. The urine contained albumin, red blood cells, polymorphonuclear leukocytes, and casts. Occasionally it was grossly bloody. The nonprotein nitrogen, creatinine, and blood urea nitrogen tended to rise.

Peripheral edema may be found, as well as changes in the eye grounds on physical examination. The patients retained a clear state of mind until a day or two before death, although some of the eclamptic patients remained comatose for the first 2 days but seemed to recover until just before death.

Pituitary Necrosis

In 1937 Sheehan[16] presented 12 new cases of pituitary necrosis in women who died post partum and collected 48 similar cases from the literature. It appeared to him to be a relatively frequent finding in women who died during the puerperium. The necrotic areas were variable in size but were restricted to the anterior lobe.

Fibrin thrombi were found in all but 2 cases, and appeared to have formed in situ. They occurred almost exclusively in the larger vessels in the upper posterior angle of the anterior lobe just beneath the stalk, and usually in several vessels close to each other. There were no possible sources for emboli in these patients, and, in the absence of any other cause for the necrosis, it seemed that the thrombosis was the primary lesion.

The necrosis seemed to date from about the time of delivery, except for one case which had its onset one day post partum, but at the time of manual removal of the placenta. The cases fell into the 2 categories of early and late, or healed, necrosis. There were 27 of the former and 21 of the latter in this collected series. It seems quite clear that the late or healed lesions represented by areas of fibrosis were actually preceded by acute necrosis which did not result in the patient's death immediately. Some of the patients with lesions of considerable size developed panhypopituitarism while others with smaller areas of necrosis did not. Hemorrhage, sepsis, and toxemia were the three important associated clinical findings. The commonest complication at delivery in both early and healed lesions was hemorrhage, which occurred in 14 of the recent and in 10 of the healed necroses. It was present in 10 of the 12 cases described by Sheehan and in 24 of the 28 cases where clinical details were available in the literature. Another important factor was "collapse" associated with the hemorrhage. In the few cases where hemorrhage was not recorded, collapse "due to other causes" occurred. Nine of the patients had retained placentas.

Five of the patients with early necrosis had eclampsia and 1 with a recent case and 1 healed with a lesion had histories of toxemia. The onset of 3 out of 4 cases dated from the period when the common treatment of eclampsia was "accouchement forcé." This frequently resulted in shock, hemorrhage, and collapse. Sheehan felt that it was doubtful that eclampsia or toxemia had any etiological significance in producing the necrosis except in predisposing to operative interference which might result in shock or hemorrhage.

Nine patients with recent and 6 with healed necrosis had histories of puerperal sepsis when the lesions began. Even in the healed group a history of sepsis was noted with more than the usual frequency. The evidence on this point was in Sheehan's opinion inconclusive, but he felt that the common association of sepsis with pituitary necrosis had a less certain etiological significance than was generally believed.

TABLE I. SUMMARY OF PATHOLOGIC

CLINICAL CATEGORY	NAME, AUTOPSY NO.	CONDITION OF FETUS AND PARITY OF MOTHER	PATHOLOGIC CATEGORY	PATHOLOGIC FINDINGS OF HEMORRHAGE,			
				LUNGS	LIVER	PITUITARY	ADRENAL
Eclampsia	E. H. 35-1	Alive i	Eclampsia	Large infarct, pneumonia	Hemorrhage Necrosis Fibrin deposits	Hemorrhage	Hemorrhage necrosis Fibrin deposits
	M. H. L. 35-23	Stb. i	Eclampsia	Broncho-pneumonia	Hemorrhage Necrosis Fibrin deposits	Negative	Negative
	E. M. S. 35-26	Alive xiv	Eclampsia	Hemorrhage	Hemorrhage Necrosis Fibrin deposits	Not available	Not available
	Y. R. 51-219	Alive i	Eclampsia	Bronchopneumonia	Hemorrhage Necrosis Fibrin deposits	Negative	Hemorrhage Necrosis Fibrin deposits
	F. S. P. 35-73	Stb. v	Eclampsia	Negative	Hemorrhage Necrosis Fibrin deposits	Negative	Hemorrhage
Toxemia with operative trauma	L. B. 31-21	Stb. i	Eclampsia	Negative	Hemorrhage Necrosis Fibrin deposits	Not available	Hemorrhage Necrosis Fibrin deposits
	H. C. O. 42-32	Alive i	Pituitary necrosis	Atelectasis emphysema	Necrosis	Hemorrhage Necrosis Fibrin deposits	Hemorrhage Necrosis Fibrin deposits
	C. L. G. 52-68	Stb. i	Lower nephron nephrosis	Negative	Necrosis	Necrosis	Negative
Premature separation of the placenta	M. P. M. 31-12	Stb. iii	Eclampsia	Broncho-pneumonia	Hemorrhage Necrosis Fibrin deposits	Hemorrhage	Negative
	E. M. K. 34-36	Stb. i	Eclampsia	Broncho-pneumonia Atelectasis, left lung	Hemorrhage Necrosis Fibrin deposits	Not available	Not available
	F. R. G. 39-15	Twins Stb. iv	Bilateral cortical necrosis	Broncho-pneumonia	Fibrin deposits	Hemorrhage Necrosis Fibrin deposits	Hemorrhage Necrosis Fibrin deposits
	M. O. H. 39-68	Stb. v	Bilateral cortical necrosis	Broncho-pneumonia	Hemorrhage Necrosis Fibrin deposits	Hemorrhage Necrosis Fibrin deposits	Hemorrhage Necrosis Fibrin deposits
	R. C. 40-62	Stb. i	Amniotic fluid embolization	Negative	Negative	Negative	Negative
	B. M. W. 40-65	Stb. i	Eclampsia	Negative	Hemorrhage Necrosis Fibrin deposits	Negative	Hemorrhage Necrosis Fibrin deposits
	E. C. S. 45-3	Stb. i	Eclampsia	Negative	Hemorrhage Necrosis	Negative	Negative

AND CLINICAL FINDINGS IN 21 CASES

NECROSIS, OR FIBRIN DEPOSITS IN ORGANS				CLINICAL FINDINGS				
KIDNEY	BOWEL	SPLEEN	OTHER	CONVULSIONS	LIFE DURATION	HEMORRHAGE	SHOCK	ANURIA
Fibrin deposits	Hemorrhage in jejunum	Negative	Fibrin deposits in heart Petechial hemorrhage in bladder	+	96 hours	0	+	+
Negative	Negative	Fibrin deposits	Healed rheumatic aorta valvulitis	0	7 hours	0	+	+
Fibrin deposits	Hemorrhage in jejunum	Negative	Fibrosis mitral valve	+	5 hours	0	+	0
Fibrin deposits	Negative	Fibrin deposits	Lower nephron nephrosis	+	11 days	+	+	+
Negative	Negative	Negative	Cerebral and subarachnoid hemorrhage	+	12 hours	0	+	+
Fibrin deposits	Negative	Fibrin deposits	Hemorrhage Necrosis Fibrin in corpus luteum	0	10 hours	+	+	+
Fibrin deposits	Colloid carcinoma of colon	Fibrin deposits	Rheumatic mitral valvulitis, healed	0	53 hours	0	+	+
Negative	Negative	Negative	Fibrin deposits in brain and basal ganglia	0	8 days	+	+	+
Negative	Negative	Negative	Subarachnoid hemorrhage	+	39 hours	0	0	0
Fibrin deposits	Negative	Not available	Subarachnoid hemorrhage	+	23 hours	0	+	0
Hemorrhage Necrosis Fibrin deposits	Hemorrhage Necrosis Fibrin deposits	Negative	Cerebral hemorrhage Ascites Hydrothorax	+	10 days	0	+	+
Hemorrhage Necrosis Fibrin deposits	Cecum hemorrhage Necrosis Fibrin deposits	Fibrin deposits	Multiple myometrial hemorrhages	+	7 days	0	+	+
Negative	Negative	Negative	Hemoperitoneum Retroperitoneal hemorrhage	0	4 hours	+	+	0
Fibrin deposits	Hemorrhage in ileum	Negative	Subarachnoid and intracerebral hemorrhage	+	6 hours	0	+	0
Negative	Negative	Hemorrhage	Hemorrhage into G.I. tract	0	29 hours	+	+	0

TABLE I—

CLINICAL CATEGORY	NAME, AUTOPSY NO.	CONDITION OF FETUS AND PARITY OF MOTHER	PATHOLOGIC CATEGORY	PATHOLOGIC FINDINGS OF HEMORRHAGE, LUNGS	LIVER	PITUITARY	ADRENAL
Hydatidiform mole with toxemia	E. V. 46-74	Mole x	Hemorrhage	Hemorrhage Necrosis Fibrin deposits	Negative	Negative	Hemorrhage Fibrin deposits
Rheumatic heart disease	M. P. 46-50	Stb. xiii	Rheumatic heart disease	Pulmonary embolus Hemorrhage Fibrin deposits	Negative	Not available	Not available
Bacterial infection	M. C. W. 33-27	Stb. v	Bacterial infection	Bronchopneumonia	Hemorrhage Necrosis Fibrin deposits	Not available	Fibrin deposits
	E. H. 46-96	Alive iii	Bacterial infection Meningitis	Pneumonia Hemorrhage Fibrin deposits	Negative	Fibrin deposits	Not available
	R. F. 49-28	Stb. i	Bacterial infection Meningococcemia	Hemorrhage Necrosis Fibrin deposits	Hemorrhage Necrosis Fibrin deposits	Not available	Hemorrhage Necrosis Fibrin deposits
Toxemia, anesthetic death	A. W. 50-64	Alive i	Cardiac arrest	Atelectasis Bronchopneumonia	Negative	Negative	Negative

Materials and Methods

The cases presented in this report were selected from the autopsied cases of maternal deaths which occurred at the Boston Lying-in Hospital, including referred cases, from 1930 through 1952. They were selected on a basis of clinical or pathological findings. All patients with toxemia, eclampsia, premature separation of the placenta, pituitary necrosis, bilateral cortical necrosis of the kidneys, and all cases with fibrin thrombi have been included in this series. The clinical records, autopsy protocols, and microscopic slides were reviewed and summarized and a partial summary is presented in Table I.

Results

Twenty-one cases were within the scope of this study. The following is a list of the various clinical categories into which these cases fell:

1. Eclampsia 5
2. Toxemia with operative trauma
   - Artificial rupture of membranes 1
   - Manual rotation 1
   - Mid-high forceps delivery 1
3. Premature separation of placenta 6
4. Amniotic fluid embolization with premature separation of placenta 1
5. Toxemia associated with hydatidiform mole and hemorrhage 1
6. Rheumatic heart disease 1
7. Bacterial infections
   - Meningitis 2
   - Pneumonia 1
8. Toxemia with death due to anesthesia 1

CONT'D

NECROSIS, OR FIBRIN DEPOSITS IN ORGANS				CLINICAL FINDINGS				
KIDNEY	BOWEL	SPLEEN	OTHER	CONVULSIONS	LIFE DURATION	HEMORRHAGE	SHOCK	ANURIA
Fibrin deposits	Negative	Negative	Ascites Right hydrothorax	0	8 hours	+	+	0
Fibrin deposits	Negative	Fibrin deposits	Hemorrhagic cystitis	0	57 hours	0	+	0
Fibrin deposits	Petechiae in stomach mucosa	Not available	Petechiae in bladder mucosa	0	36 hours	0	+	0
Fibrin deposits	Negative	Not available	Pneumococcus Type 23	0	24 hours	0	+	0
Fibrin deposits	Hemorrhage into G.I. tract mucosa	Hemorrhage Fibrin deposits	Fibrin deposits in heart, pancreas, lymph node	0	12 hours	0	+	0
Negative	Negative	Negative	Anoxic encephalopathy	0	2 hours 22 minutes	0	+	0

Certain pathologic findings and associated clinical phenomena are presented in Table I.

The information presented in the table has focused attention on hemorrhage, necrosis, and fibrin deposition. The last case is included only as a "control" case of uncomplicated toxemia.

Clinical Findings

The duration of life in all these patients, from the onset of the acute disease process, varied from 4 hours to 11 days. Clinical hemorrhage occurred in 6 out of 20 cases. Shock developed in every case save one and anuria was found in 9 out of 20.

All the patients with eclampsia had some degree of shock except one (A-35-1), who had a cesarean section and lived 4 days. Four of the 5 eclamptic patients developed anuria and one developed severe hemorrhage.

Two of the 3 toxemic patients with operative trauma had hemorrhages and all developed shock and anuria. All but one of the 7 patients with premature separation of the placenta went into shock, while 2 developed anuria and 2 showed a hemorrhagic tendency.

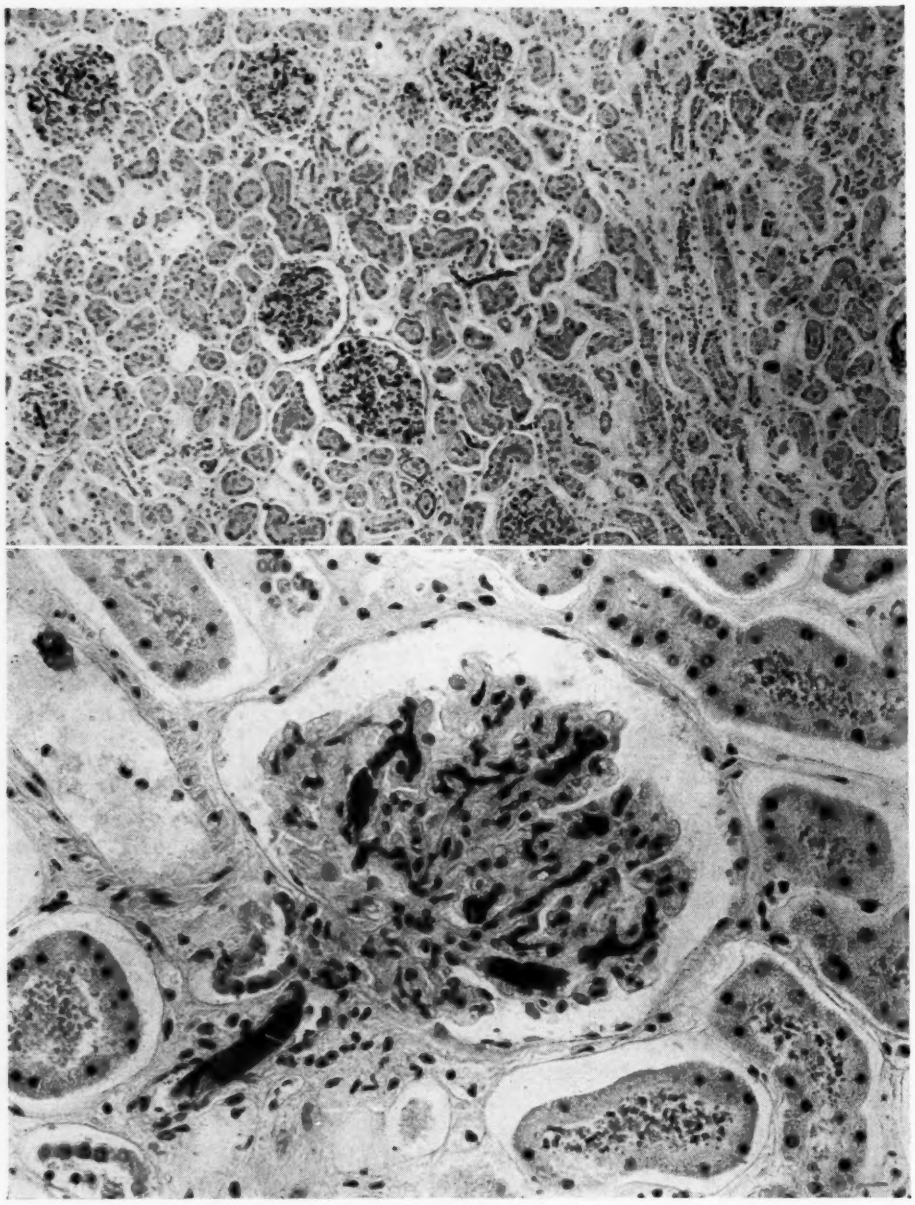
The patient with toxemia and a hydatidiform mole developed hemorrhage and shock and died within 8 hours. The patient lived too short a time to exhibit anuria. Shock alone was found in the patient with active rheumatic heart disease. The patients with bacterial infections all had shock and one developed anuria, but none presented clinical hemorrhages.

Pathology

Several points of interest were demonstrated by this group of autopsied patients. They illustrate the fact that there is considerable overlapping of

the clinical and pathological entities that previously were thought of as separate conditions. For example, pituitary necrosis occurred in association with the clinical syndrome of eclampsia and with the pathologic entity of bilateral

A.



B.

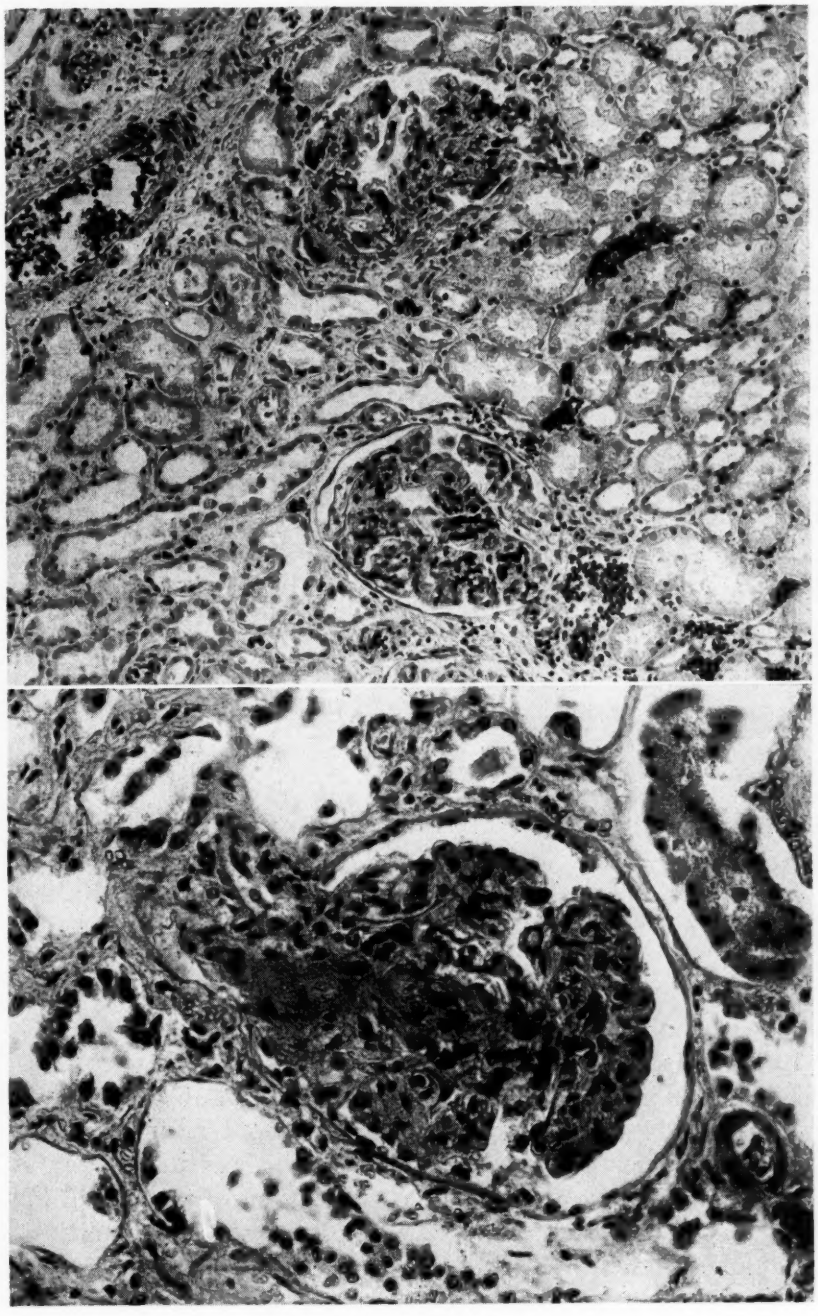
Fig. 1.—Kidney.

A, Fibrin thrombi deposited in practically every glomerulus and in a few intertubular capillaries. No necrosis or hemorrhage. Hydatidiform mole with toxemia and hemorrhage. A-46-74. (Methylene blue stain. ×100. Reduced one-fifth.)

B, Fibrin thrombi in precapillary arteriole and glomerular capillary. Hydatidiform mole with toxemia and hemorrhage. A-46-74. (Phloxine methylene blue. ×400. Reduced one-fifth.)

cortical necrosis. Periportal fibrin deposition with hemorrhage and necrosis, characteristic of eclampsia, was found in patients without convulsions, in those

A.



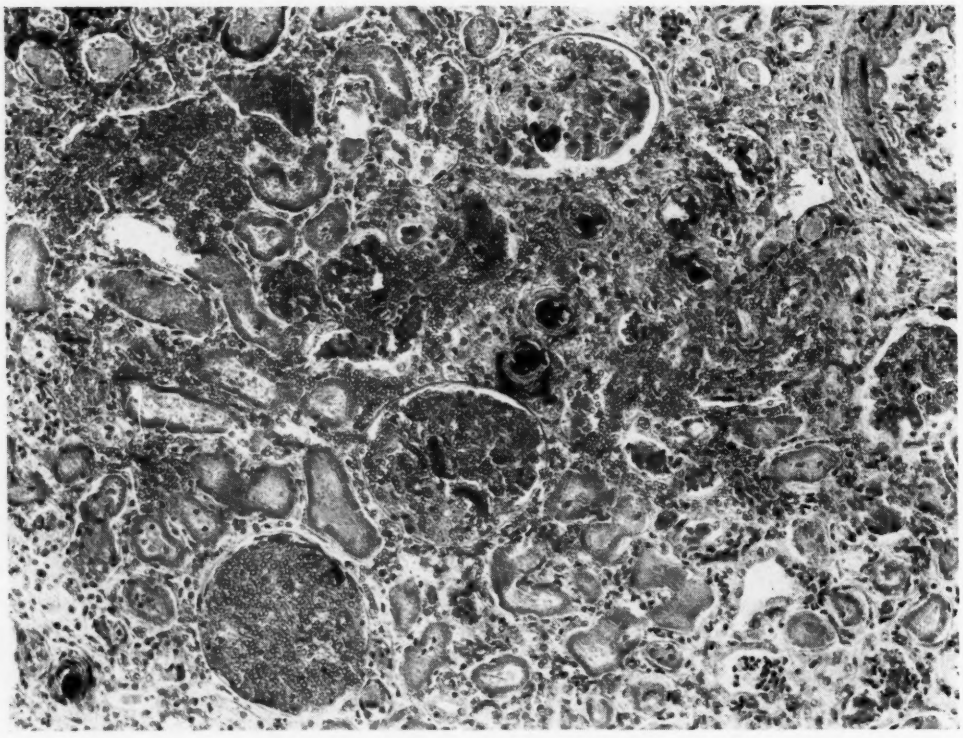
B.

Fig. 2.—Kidney.

A, Fibrin thrombi in 2 glomeruli in a patient with eclampsia and manual removal of placenta. A-31-21. (Eosin methylene blue stain. ×200. Reduced one-fifth.)

B, Fibrin thrombi in precapillary arteriole of glomerulus in patient with eclampsia. A-35-26. (Phloxine methylene blue. ×400. Reduced one-fifth.)

with bilateral cortical necrosis, and even in patients with bacterial infections with no evidence of pre-existing toxemia. The fibrin thrombi occluding the glomerular capillaries, seen characteristically in bilateral renal cortical necrosis, were often found in patients with the clinical syndrome of eclampsia and in those with bacterial infections only. From the clinical standpoint there was also overlapping, inasmuch as patients with premature separation of the placenta and bilateral renal cortical necrosis had convulsions which are usually associated with eclampsia.



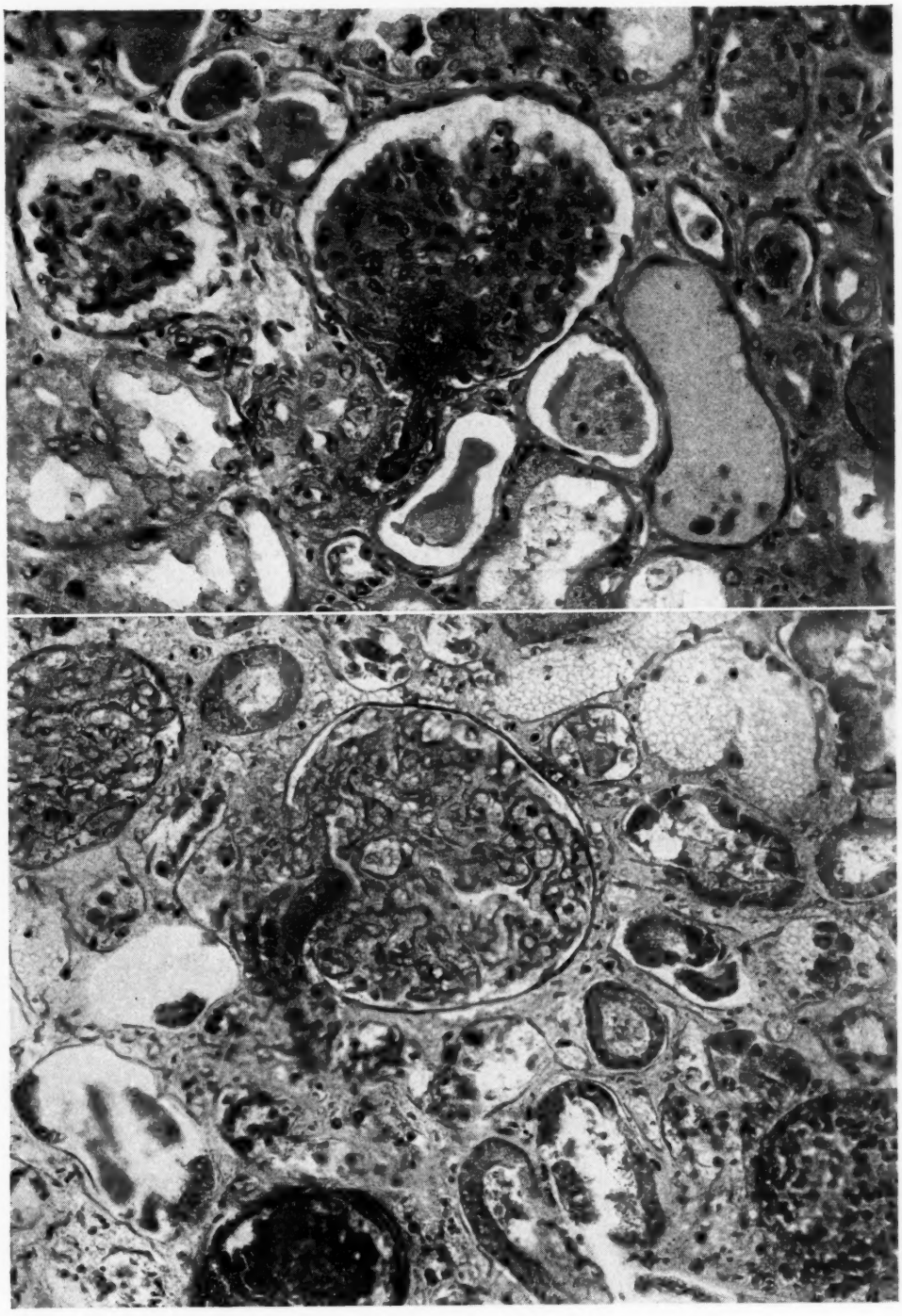
A.

Fig. 3A.—Kidney. Fibrin thrombi in glomerular capillaries and intralobular arterioles at the edge of an area of necrosis. Bilateral cortical necrosis of the kidneys. A-39-68. (Phloxine methylene blue. ×200. Reduced one-fifth.)

Of 10 patients with the clinical or pathological syndromes of eclampsia, 9 had fibrin thrombi in one or more organs. Also, of 16 patients with a pre-existing toxemia, 14 exhibited fibrin thrombi in one or more viscera. It is clear that fibrin thrombi in the small vessels can be found in the great majority of patients who die of the acute complications of toxemia of pregnancy. In view of the focal nature of the lesion, it is possible that multiple sections from all viscera might reveal these thrombi in an even higher percentage of cases. These findings, in combination, suggest that fibrin thrombosis is the basis of the pathologic changes in all these syndromes.

In general the thrombi were found in vessels of small caliber, of the size of capillaries and precapillary arterioles. They were present in the vessels of the greater circulation. The hepatic arterioles, the central arterioles of

B.



C.

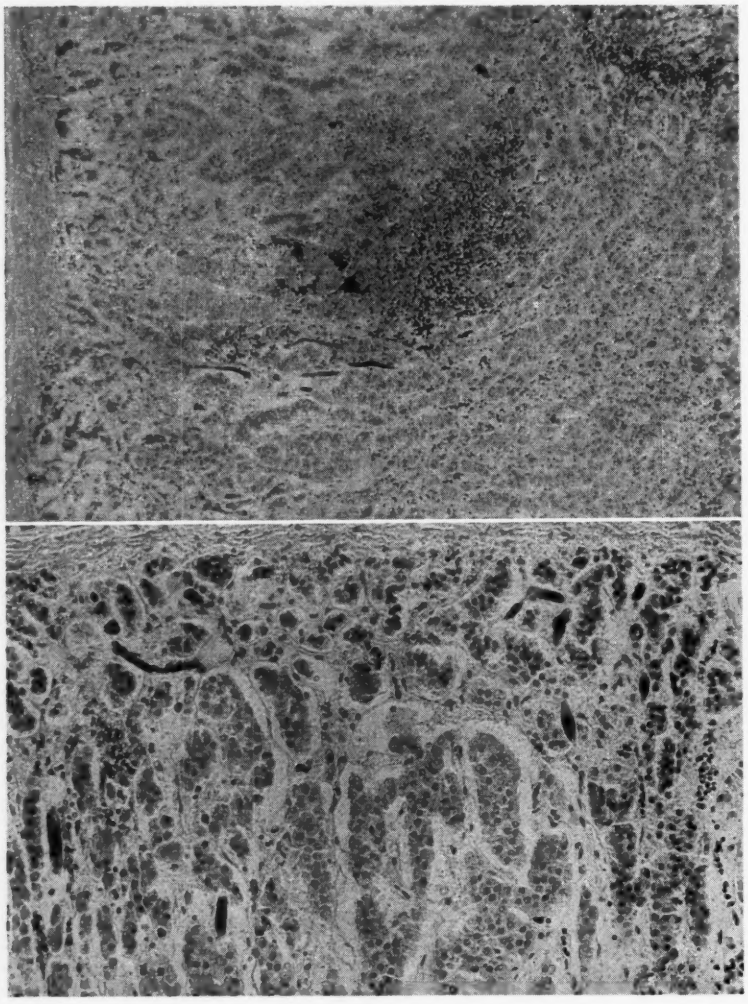
Fig. 3, *B* and *C*.—Kidney.

B, Fibrin thrombi occluding precapillary arteriole in an area away from the zone of infarction. Bilateral renal cortical necrosis. A-39-15. (Phloxine methylene blue. ×400. Reduced one-fifth.)

C, Fibrin thrombi occluding the lumen of an infarcted glomerulus. All the tissue in this field is completely infarcted. Bilateral renal cortical necrosis. A-39-15. (Phloxine methylene blue. ×400. Reduced one-fifth.)

the white pulp of the spleen, the precapillary arterioles of the kidney, and the afferent vessels of the stalk of the pituitary were most commonly involved (Figs. 1 to 18). In most instances they were associated with hemorrhage or necrosis or both, demonstrating that they represent antemortem thrombi and

A.



B.

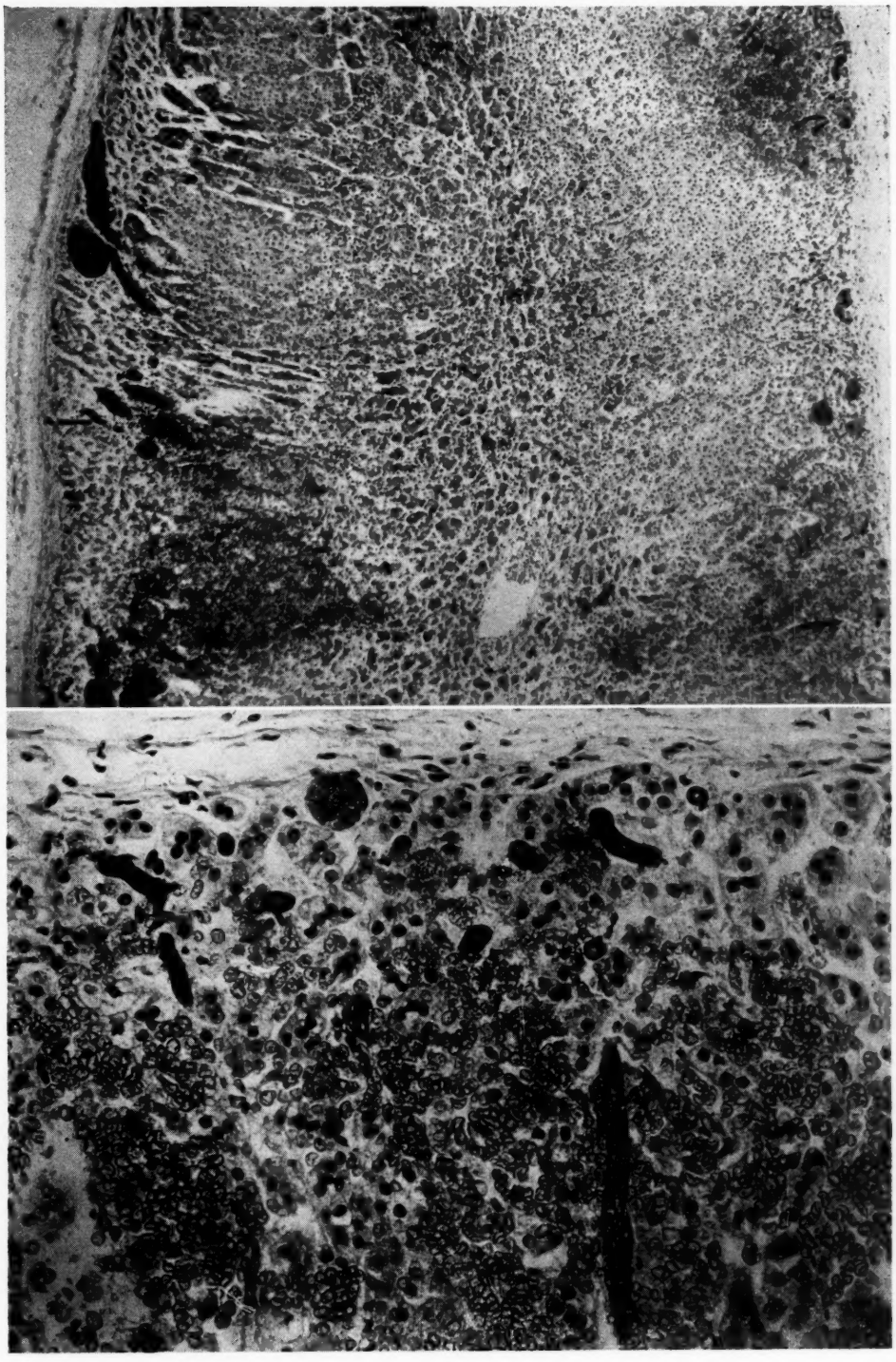
Fig. 4.—Adrenal.

A, Fibrin thrombi in sinusoids of the zona glomerulosa and outer fasciculata. A small hemorrhage is seen distal to the thrombi. Hydatidiform mole with toxemia and hemorrhage. A-46-74. (Phloxine methylene blue. ×100. Reduced one-fifth.)

B, Fibrin thrombi in sinusoids of the zona glomerulosa. No hemorrhage or necrosis. Hydatidiform mole with toxemia and hemorrhage. A-46-74. (Phloxine methylene blue. ×200. Reduced one-fifth.)

not merely postmortem clots. In many cases they were unassociated with hemorrhage or necrosis of the organ, but, in these cases, hemorrhage and necrosis were invariably found associated with fibrin thrombi in other organs. In 2 cases, C. L. G. (A-52-68) and E. C. S. (A-45-3), hemorrhage and necrosis

A.



B.

Fig. 5.—Adrenal.

A, Multiple areas of hemorrhage and necrosis associated with fibrin deposits under the capsule of the adrenal in a patient with eclampsia. A-31-21. (Phloxine methylene blue. ×90. Reduced one-fifth.)

B, Fibrin thrombi in sinusoids of zona glomerulosa with associated hemorrhage in patient with eclampsia. A-31-21. (Phloxine methylene blue. ×400. Reduced one-fifth.)

were found in the absence of fibrin thrombi. The possibility that thrombi may have been present and then destroyed by a fibrinolysin will be discussed subsequently.

The fibrin thrombi in these cases are of a special nature and consist of strands and homogeneous masses of fibrin, in most instances occluding the lumen of the vessel. In some larger arterioles, however, fibrin forms a coat lining the vessel wall and thins out toward the center. Only rarely can red cells, white cells, or platelets be found in the thrombi, which set them apart from the usual antemortem thrombi of large vessels and from postmortem clots. They give the appearance, not of emboli, but of thrombi which have formed "in situ."

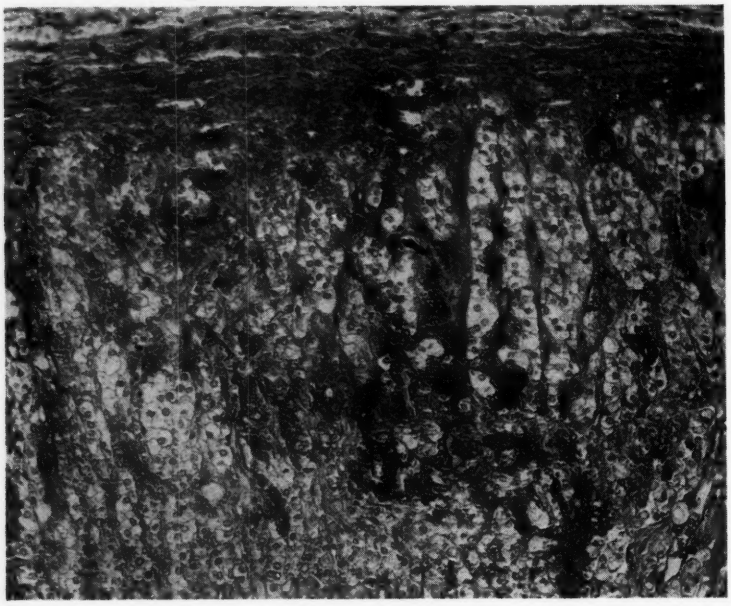


Fig. 6.—Adrenal. Fibrin deposits and hemorrhage in zona glomerulosa and fasciculata in a patient with bilateral renal cortical necrosis. A-39-15. (Phloxine methylene blue. ×200. Reduced one-fifth.)

All patients except A. W. (A-50-64) showed either hemorrhage, necrosis, or fibrin deposition in varying combinations in one or more of the viscera. A. W. was a patient with toxemia who died as a result of anoxic encephalopathy during the administration of spinal anesthetic. Excluding this patient, the most frequently involved organ in the remaining 20 cases was the kidney. Fibrin thrombi were present in 14, with associated necrosis and hemorrhage in 2, and no pathologic change was observed in 6. The liver exhibited fibrin thrombi in 13 cases, necrosis in 15, hemorrhage in 13, and in 4 was normal. Fibrin thrombi were found in 10 adrenals, with necrosis in 8, hemorrhage in 10; 5 were normal and 4 were unavailable for examination. The spleen had fibrin thrombi in 7 cases, hemorrhage in 2, necrosis in none, and 9 spleens were normal. In 2 cases the spleen was unavailable.

The pituitaries in 4 cases had fibrin thrombi, necrosis in 3, and hemorrhage in 5. Seven were negative and 6 were unavailable for examination. Hemorrhages, usually of the size of petechiae, were found in the gastrointestinal tract in 6 cases, but fibrin thrombi and necrosis in only 2, while in 15 no hemorrhages were found. Fibrin thrombi were present in the lung in 4 cases, hemorrhage in 5, and necrosis in none. Six lungs were negative. Several lungs were encountered with thrombi in the larger vessels, but it could not be determined with certainty that these were not postmortem clots. Hemorrhage in the brain was found in 6 cases, but fibrin thrombi in only 3 cases. Fibrin thrombi were found in the myocardium in 2 instances.

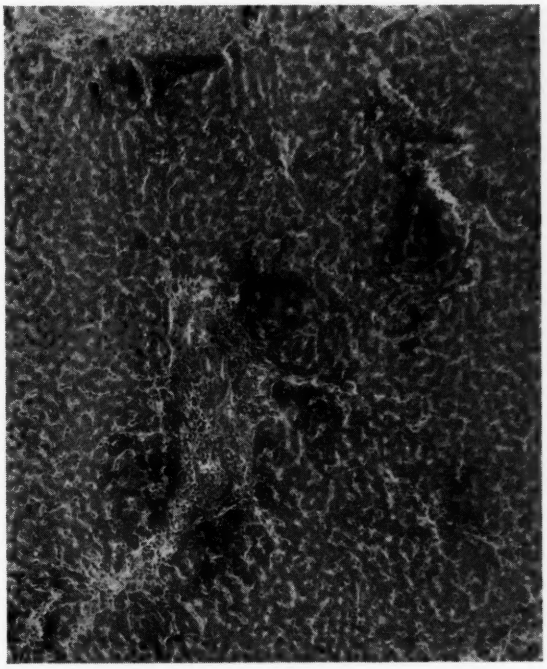


Fig. 7.—Liver. Fibrin deposits in hepatic arterioles and in periportal sinusoids. Except for hemorrhage in these regions, the liver tissue is otherwise essentially normal. Toxic separation of the placenta and eclampsia. A-31-12. (Phloxine methylene blue. ×100. Reduced one-fifth.)

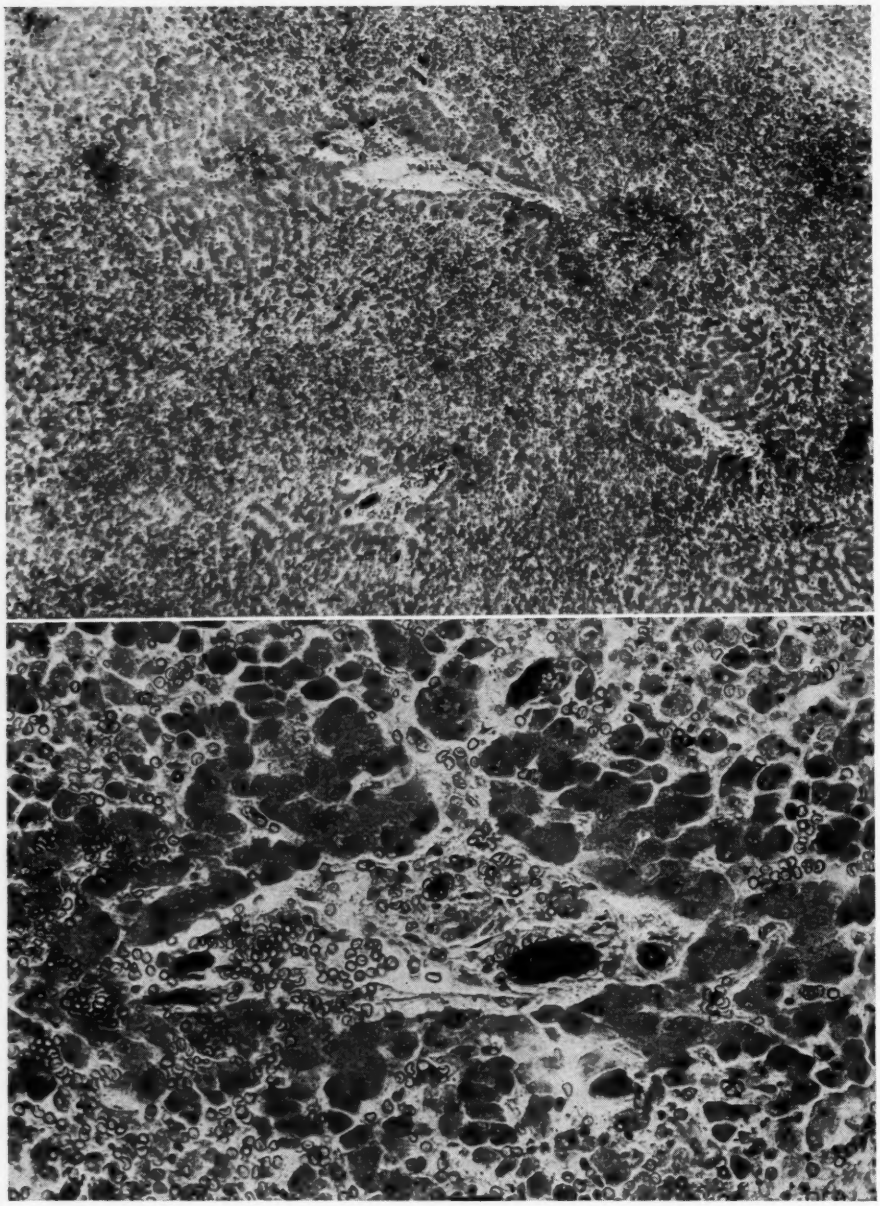
Large amounts of fluid in the serous cavities were commonly found in this series. In several there was extravasation of a large amount of blood into the peritoneal cavity. Bronchopneumonia was a frequent finding and appeared to be terminal in most cases. Active rheumatic heart disease was encountered once, as was healed rheumatic mitral valvulitis. There were 2 cases of bilateral cortical necrosis of the kidneys (previously reported by Sheldon and Hertig[17]), and 2 cases of lower nephron nephrosis.

Uncomplicated Toxemia

One point deserves emphasis, namely, that the pathologic changes in uncomplicated toxemia are to be differentiated from the pathologic changes in eclampsia and the other acute disasters discussed in this paper. Although the

pathologist's opportunities to examine tissue from patients with uncomplicated toxemia are quite rare, the one case in this series that fits this category is Mrs. A. W. (A-50-64), a patient who had toxemia, but who died as the result of spinal anesthesia. This patient exhibited none of the changes such as fibrin

A.



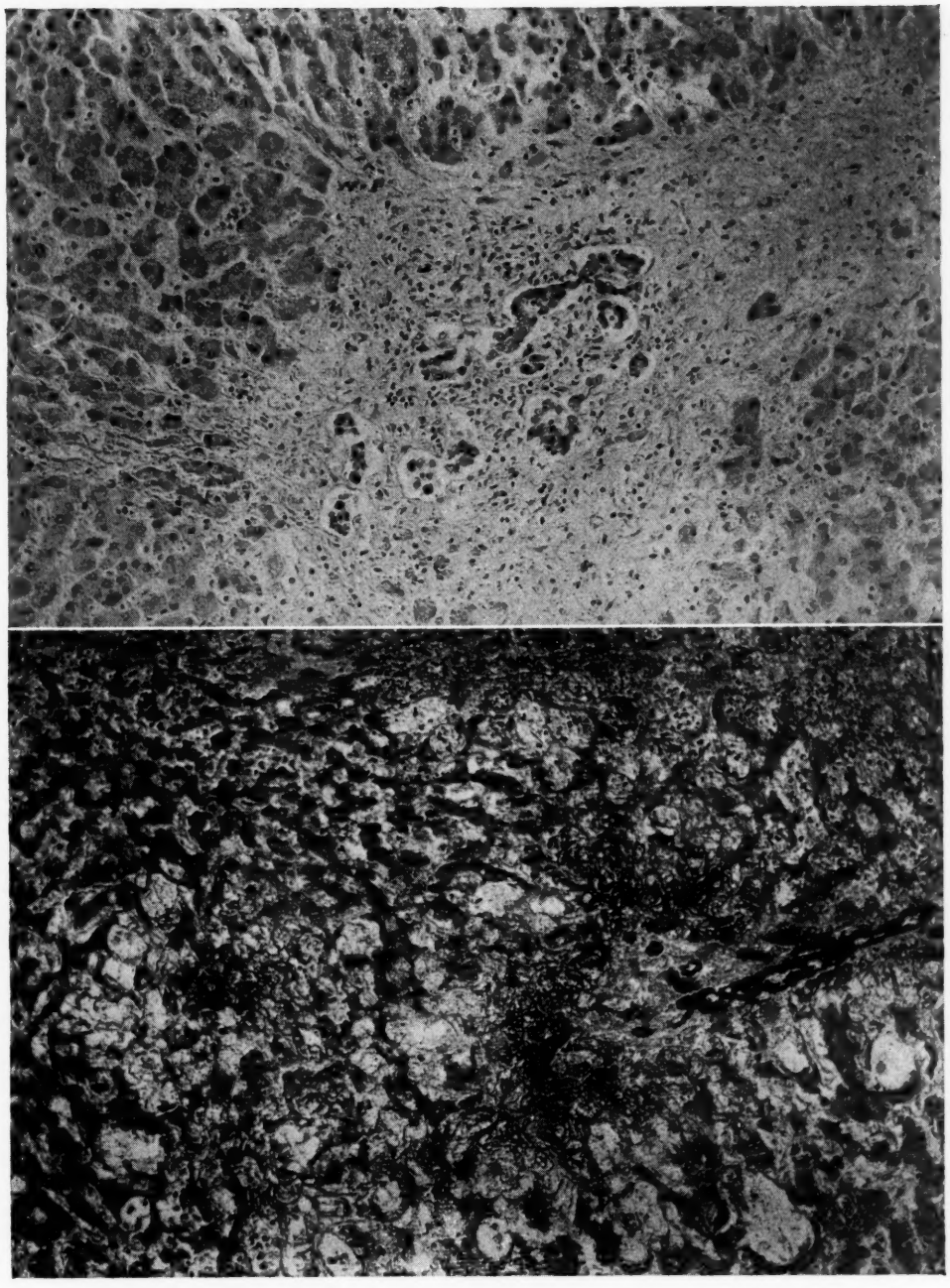
B.

Fig. 8.—Liver.

A, Fibrin thrombi in hepatic arterioles in portal connective tissue. Hemorrhage and early necrosis of large confluent area of liver tissue. Eclampsia with manual removal of placenta. A-31-21. (Phloxine methylene blue. ×100. Reduced one-fifth.)

B, Fibrin thrombi in hepatic arterioles in patient with eclampsia. A-31-21. (Phloxine methylene blue. ×400. Reduced one-fifth.)

A.



B.

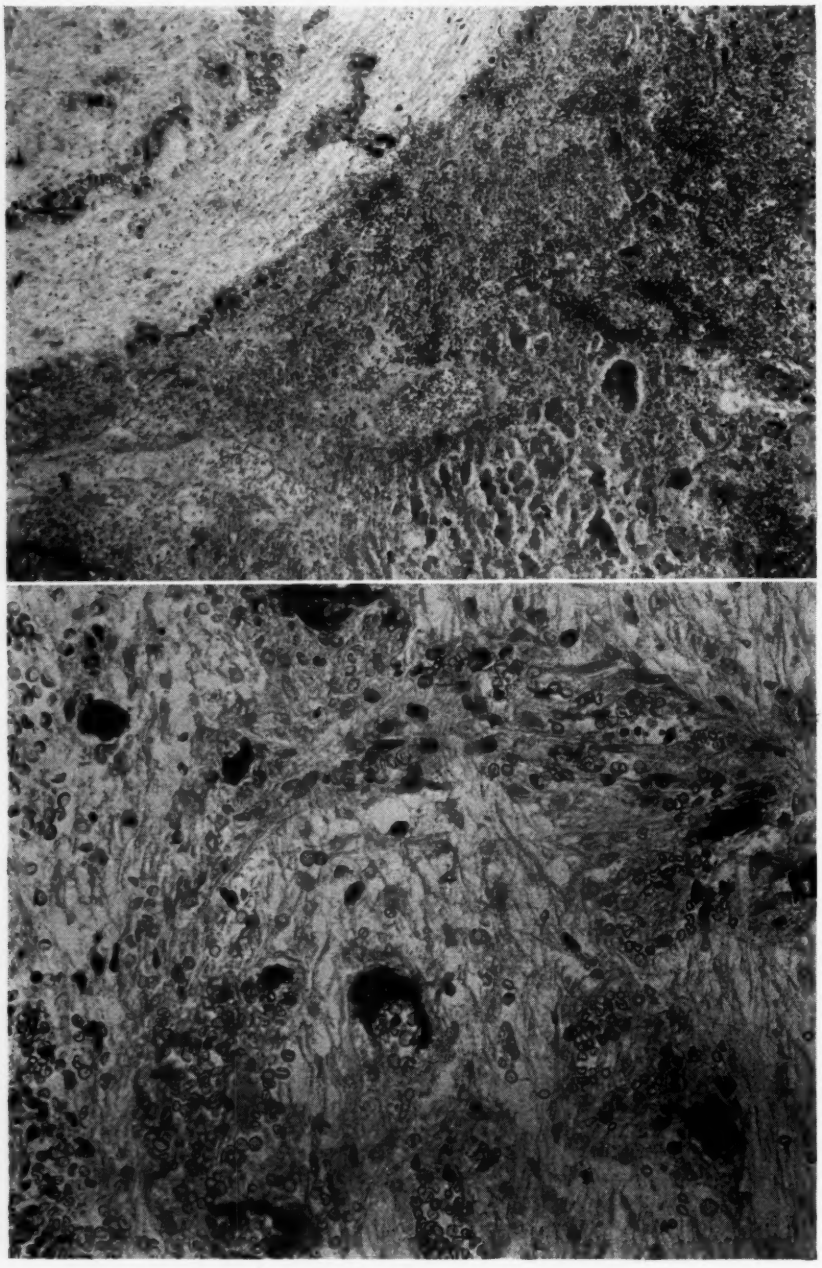
Fig. 9.—Liver.

A, Periportal region showing evidence of previous necrosis. The liver cells have been destroyed and all that remains is a condensed reticulum with a few inflammatory cells. Eclampsia with survival for 8 days. PBBH A-52-68. (×200. Reduced one-fifth.)

B, Dilation of sinusoids with hemorrhage and early necrosis of liver cells with early inflammation. The fibrin deposits can be traced from the hepatic arterioles in the portal connective tissue out into the periportal sinusoids. Postpartum eclampsia. PBBH A-51-219. (Phloxine methylene blue. ×400. Reduced one-fifth.)

deposition, hemorrhage, and necrosis that are related to eclampsia, bilateral cortical necrosis, and pituitary necrosis. A similar autopsied case of uncomplicated toxemia was reported by Teel, Reid, and Hertig.[22]

A.



B.

Fig. 10.—Pituitary.

A, The posterior lobe is above and to the left. The stalk enters at the left. The anterior and intermediate lobes are hemorrhagic and infarcted with only one small patch of uninvolved tissue remaining. The vessels of the posterior lobe and the stalk are occluded by fibrin thrombi. Eclampsia. A-42-32. (Phloxine methylene blue. ×100. Reduced one-fifth.)

B, Fibrin thrombi and associated focal hemorrhages of posterior lobe of pituitary. Eclampsia. A-42-32. (Phloxine methylene blue. ×400. Reduced one-fifth.)

One of the best pieces of work supporting this idea is to be found in the liver biopsy studies of Ingerslev and Teilum.[9] These authors found fibrin deposition, hemorrhage, and necrosis in the livers of only those patients with eclampsia, and in none of the patients with toxemia or pre-eclampsia.

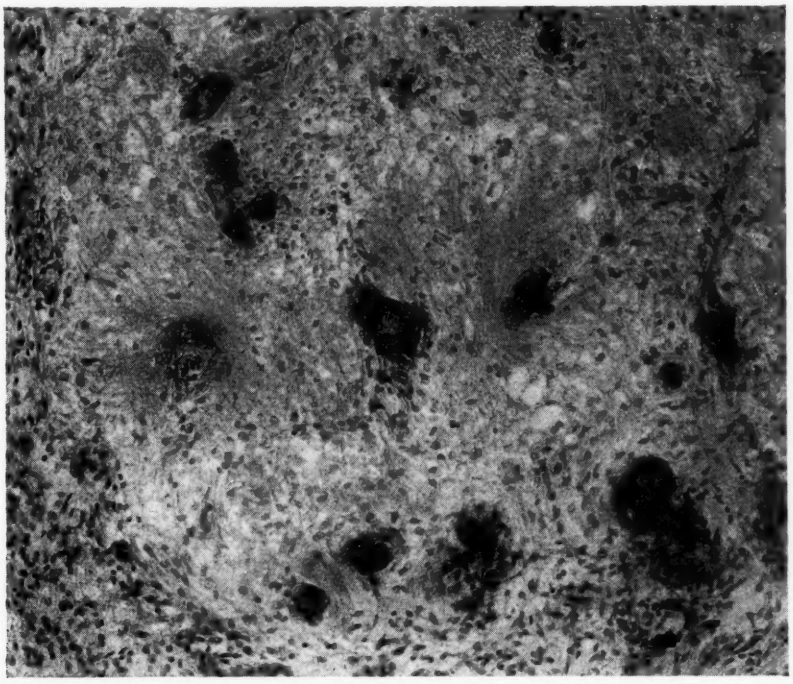


Fig. 11.—Mid-brain. Fibrin thrombi with associated focal hemorrhage and necrosis in tuber cinereum. Bilateral renal cortical necrosis. A-39-15. (Phloxine methylene blue. ×200. Reduced one-fifth.)

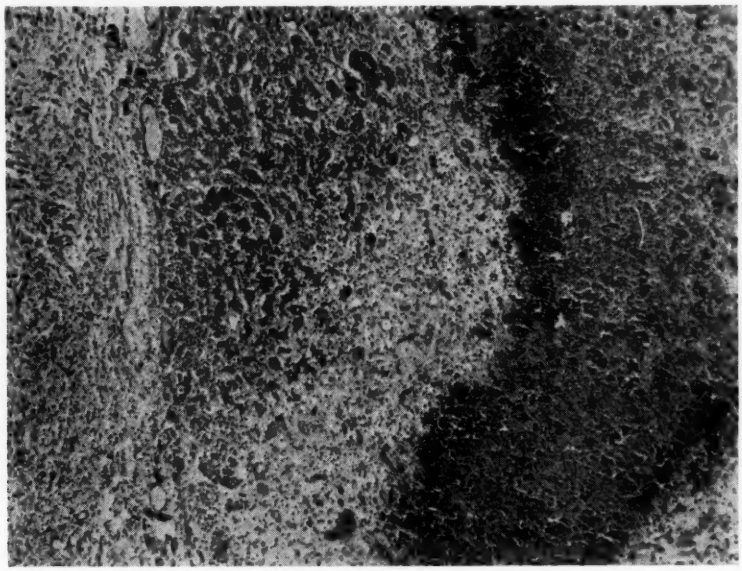
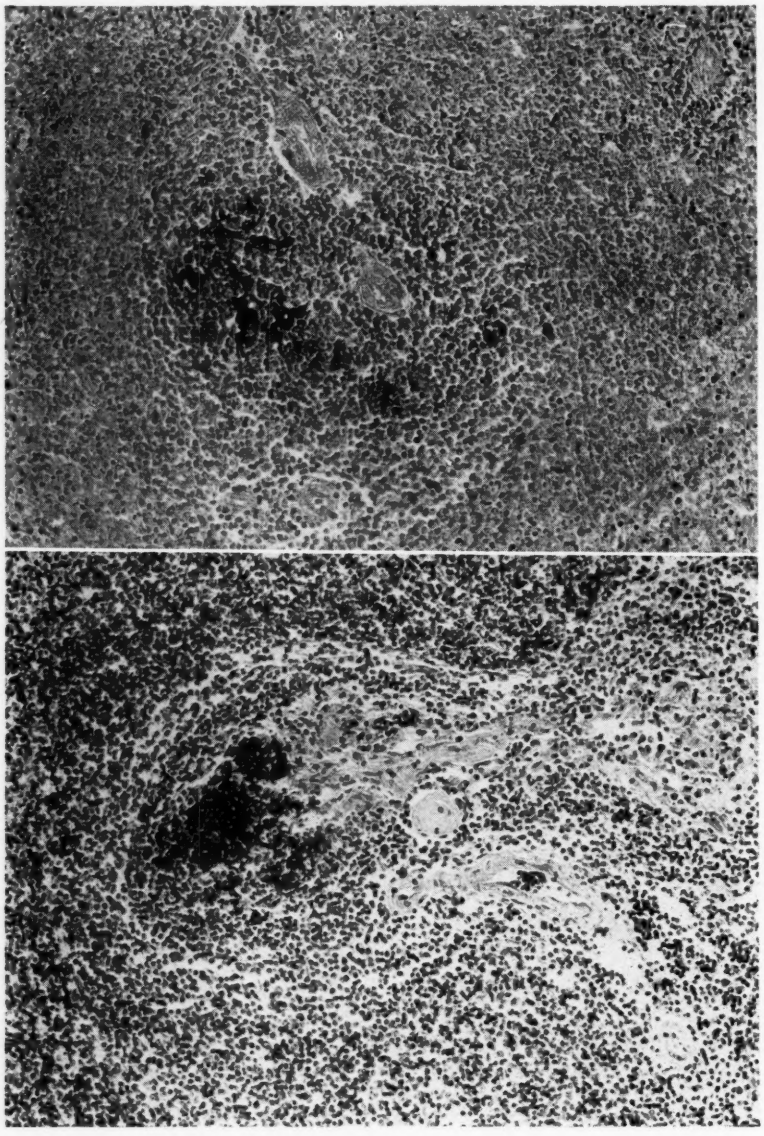


Fig. 12.—Pituitary. Area of infarction of anterior lobe in eclampsia. The dark zone around the infarct appears to be calcification. PBBH A-52-68. (×75. Reduced one-fifth.)

Since toxemia is usually a disease of several weeks' duration rather than an acute process, one logically looks for pathologic changes which might be associated with such a long-standing condition. The changes of this nature which seem most likely to be those of pure toxemia are largely confined to the kidney. These consist of thickening of the basement membrane in the glomerular capillaries, swelling of the cells of the visceral layer of Bowman's capsule (with accumulation of fat and glycogen), and rarely "hyaline droplets"

A.



B.

Fig. 13.—Spleen.

A, Meshwork of fibrin in Malpighian corpuscle in patient with eclampsia. A-42-32. (Phloxine methylene blue. ×200. Reduced one-fifth.)

B, Extravasated fibrin in Malpighian corpuscle in patient with eclampsia. A-31-21. (Phloxine methylene blue. ×200. Reduced one-fifth.)

in the tubular epithelium. These latter have been associated with increased protein reabsorption by the tubules by Jean Oliver.[11] These changes in addition to those in the placenta and decidua are of a type which one might as-

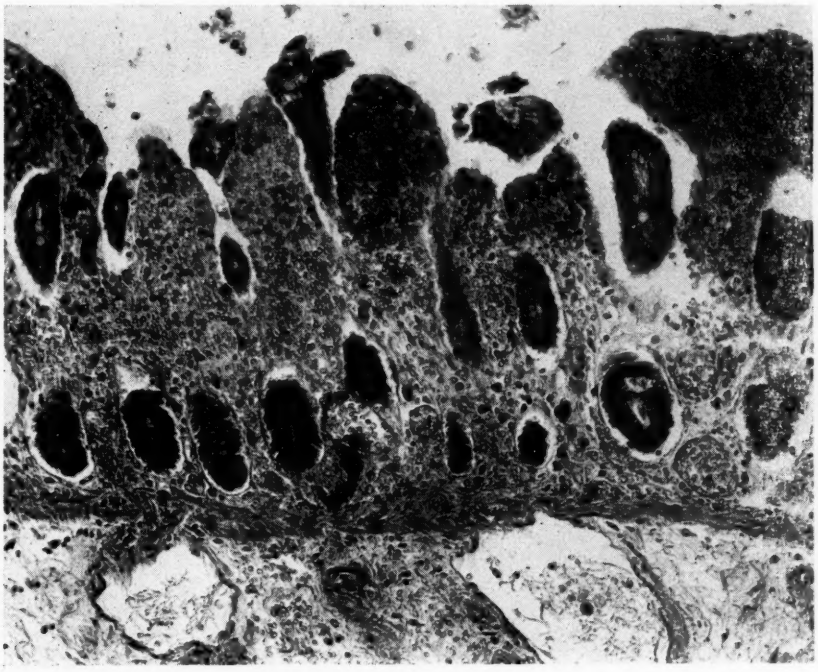


Fig. 14.—Cecum. Hemorrhage into the mucosa with fibrin thrombi in arterioles in muscularis mucosae. Bilateral renal cortical necrosis. A-39-15. (Phloxine methylene blue. ×200. Reduced one-fifth.)

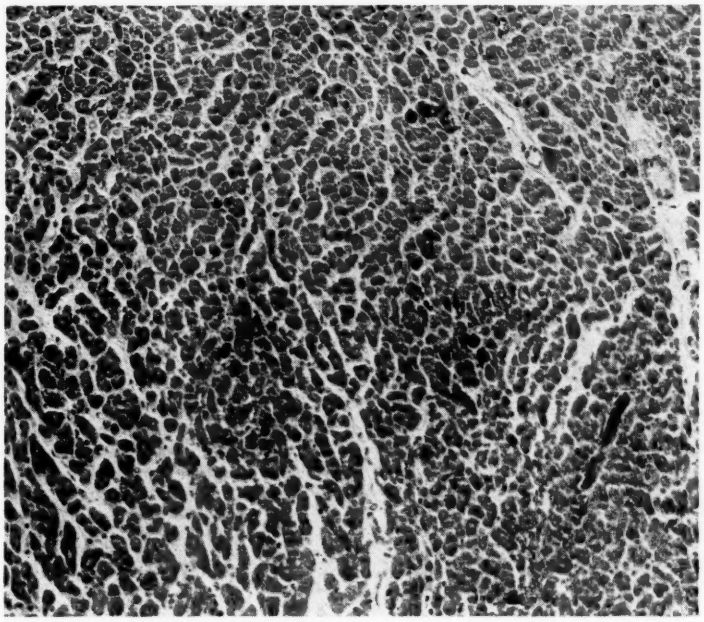


Fig. 15.—Heart. Fibrin thrombi deposited in myocardial capillaries. The cardiac muscle in this region is not necrotic and there are no hemorrhages. A-49-28. (Phloxine methylene blue. ×100. Reduced one-fifth.)

sociate with a condition of a few weeks' duration and are of a minor sort in comparison with the pathologic changes in the patients with eclampsia and those with renal cortical necrosis.

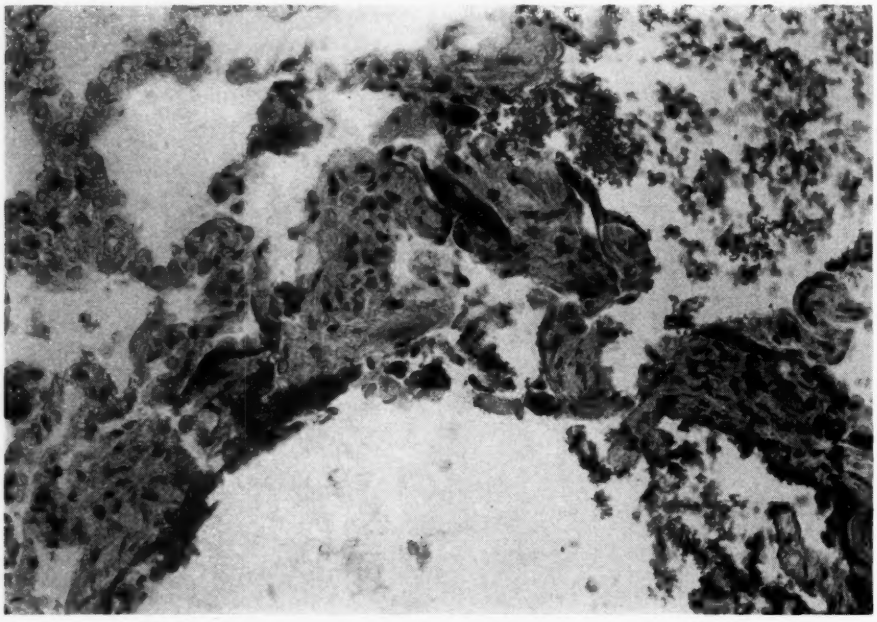


Fig. 16.—Lung. Fibrin thrombi in alveolar capillary with focal extravasation of fibrin. Meningitis and pneumonia caused by pneumococcus. A-46-96. (Phloxine methylene blue. ×400. Reduced one-fifth.)

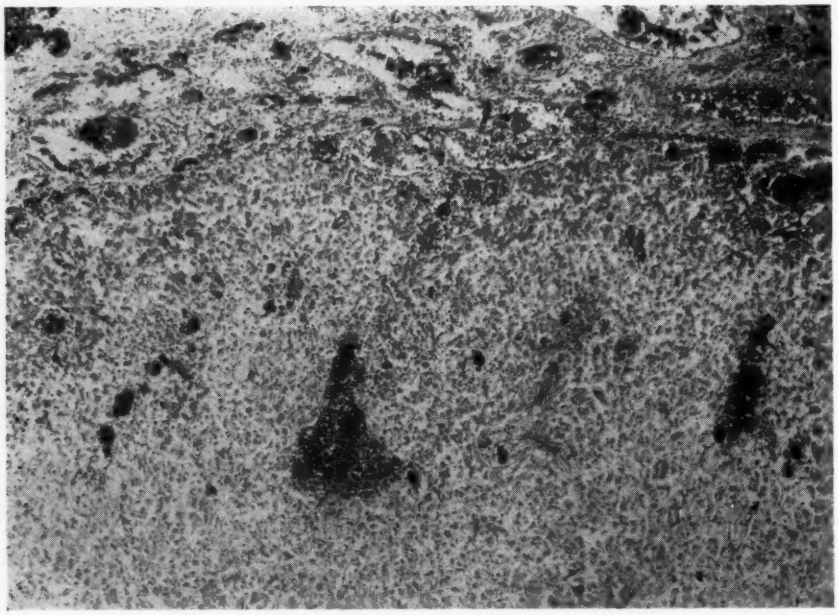


Fig. 17.—Corpus luteum. Fibrin thrombi in peripheral vessels of corpus luteum with infarction of the center. Eclampsia. A-31-21. (Phloxine methylene blue. ×90. Reduced one-fifth.)

Sheehan[15] supports this idea and also states that these are two conditions closely related but not identical. The second may be merely a severe degree of one aspect of the first, but there are sufficient differences to warrant considering them separately.

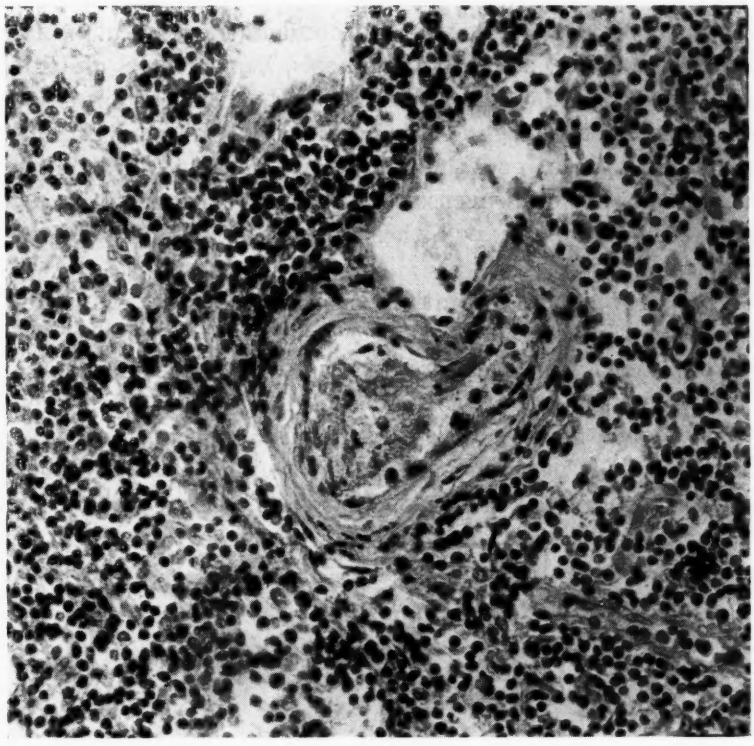


Fig. 18.—Lymph node. Fibrin thrombus in arteriole of lymph node. A-49-23. (Phloxine methylene blue. ×400. Reduced one-fifth.)

He divides them as follows:

A. Ordinary toxemia consisting of the hypertension-albuminuria-edema complex, a prolonged functional disturbance with very little histological abnormality to be found in the organ.

B. An acute pathologic disturbance of function (particularly cerebral, but also in other places). It usually develops in patients who have "A"; in them it may develop gradually, giving the picture of severe pre-eclampsia with headache, eye symptoms, abdominal pain, or it may occur with great suddenness. Rarely, it occurs in patients who have not had "A"—fulminating eclampsia or some abruptio placentae.

Placental Changes

The pathologic changes in the placenta and decidua deserve mention since these 2 tissues may play a large part in the production of toxemia and eclampsia.

The placentas of toxemic and eclamptic patients frequently contain infarcts of varying size, some being visible only under the microscope and others

occupying large portions of the placenta grossly. Large masses of laminated clot, intervillous thrombi, are often present. One of the most consistent changes, which was originally described by Tenney,[23] is the appearance of excess numbers of clumped syncytial nuclei (syncytial knots). This change represents in general a premature aging of the syncytial trophoblast.

An equally frequent change can be found in the decidua, particularly the decidua basalis, and this consists of necrosis, hemorrhage, and infiltration of polymorphonuclear leukocytes. The hemorrhage is often associated with thrombosis of one of the large decidual sinusoids which are for the most part lined by a single layer of endothelium and surrounded by decidua. While a minimal amount of decidual necrosis and/or hemorrhage can be found in the decidua basalis in any pregnancy, these changes are much more prominent in toxemia and eclampsia.

Two types of vascular alteration may also be present in the decidua in toxemia or eclampsia (Hertig[8]). These consist of a so-called "fibrinoid degeneration" of the walls of the spiral arterioles and atherosclerosis of the same vessels. These changes may be found separately or in the same vessel, and when fully developed may result in thrombosis of the vessel with organization of the thrombus. It is possible that the narrowing and occlusion due to these changes are responsible for the marked necrosis of the decidua, and in turn for the occurrence of premature separation of the placenta. In this series of patients, placental or decidual changes were observed only in the patients with toxemia or eclampsia and not in others.

Comment

Defibrination in Clinical Cases.—

Certain hematologic observations in patients with clinically recognizable premature separations of the placenta add considerable support to the idea that intravascular fibrin deposition is a major event in the condition described above. A clotting defect traceable to a decrease or complete lack of fibrinogen in the blood has been demonstrated by Reid[12] in patients with premature separation of the placenta, in both toxic and nontoxic varieties. In both types of separation there is (a) a decrease in the clotting ability of the blood, (b) afibrinogenemia, (c) hypoprothrombinemia, and (d) occasionally a circulating fibrinolysin. This author has demonstrated that the fibrinogen content of the blood may show a precipitous drop. The sudden disappearance of fibrinogen does not apparently result from liver insufficiency, since most of the patients have normal liver function. The complication of defibrination was associated with toxemia in some cases but was also found in nontoxic individuals. Uncontrollable hemorrhage is a common phenomenon in many, but not all, of these patients.

The cause of the observed afibrinogenemia and hypoprothrombinemia must remain speculative. It has been suggested that the sudden loss of fibrinogen is due to the intravascular deposition of this substance in the form of fibrin. The cases presented in this report lend considerable support to this idea, since most of them had intravascular deposits of fibrin.

Reid[12] has suggested that the products of pregnancy, whether fetal or maternal, must bear some causal relationship. It would appear that a substance from the uterine contents which has the ability to remove fibrinogen from the blood is released into the maternal circulation.

Fibrinogen digestion by a fibrinolytic enzyme is another possible mechanism for producing the afibrinogenemia. Tagnon[25] has shown that a precursor of fibrinolysin is present in all blood and that it becomes activated by shock and hemorrhage. His observation that the lung contains an activator for the fibrinolytic enzyme system is of interest. The escape of substances from the uterus might well irritate the parenchymal tissue of the lung to release additional fibrinolytic enzyme.

The development of fibrinolysins following shock and hemorrhage might well explain the absence of fibrin thrombi in the 2 cases, C. L. G. (A-52-68) and E. L. S. (A-45-3), in our autopsy series.

Following the defibrination process the fibrinogen level in patients who survive may return to normal in 1 to 3 days. Schneider[14] has reported 2 cases of partial defibrination of the blood in patients with intrapartum eclampsia. These patients restored their fibrinogen not only to normal levels, but to the high levels of severe toxemia and of the postpartum interval. These patients did not receive transfusions and therefore the restoration of fibrinogen must have been accomplished by the patients' own livers. Schneider further pointed out that some of his eclamptic patients had retroplacental hematomas suggestive of premature separation of the placenta.

Experimental Work.—

Schneider[14] has developed the hypothesis that the basic pathologic-physiologic change in eclampsia or premature separation is a sudden, acute injection into the maternal blood stream of thromboplastin derived from the decidua or placenta. The decidua especially has a very high thromboplastic activity when compared with that of other tissues of the body. Using extracts of human decidua from the maternal surface of the placenta, he was able to produce convulsions and death in mice by intravenous injection. The response of the animals was prompt and resulted in death or prompt recovery. Death appeared to be due to circulatory failure with a complete cessation of blood flow in the peripheral circulation. This occurred even with sublethal doses, but with such doses the blood soon began to pulsate and flow again and the animals returned to normal activity.

Pathologically, the animals that died immediately presented evidence of obstruction of the *lesser circulation* with distention of the liver and dilation of the chambers of the right side of the heart. Microscopically there was a disseminated "thrombo-embolism" of the pulmonary arterial vasculature. The structure of these thrombi suggested a differential deposition of fibrin under dynamic conditions. The fibrin deposits were not limited to the lesser circulation but were found also in the brain in occasional animals. Small foci of hemorrhage and necrosis were sometimes associated with these thrombi. Foci of necrosis were observed also in the liver and a hemorrhagic tendency was

noted in some animals. Strangely enough, the pulmonary thrombi were rare or absent among the animals that survived, including those which exhibited severe reactions to the injections. Only the animals that died immediately exhibited thrombi constantly.

That thrombi may form and then quickly lyse in vivo is indicated by the work of Green and Stoner.[6] In the rat, following known, near-lethal doses of clotting agent, in combination with nucleotides, thrombi may be very extensive in surviving animals and yet disappear rapidly during the next 24 hours. In addition, Heard[7] has shown in the rabbit that, under similar conditions, and after the intravenous injections of large numbers of blood clots, complete fibrinolysis occurs very rapidly.

Schneider[14] states that the animals injected with thromboplastin were deficient in fibrinogen following the injection, and that this deficiency was due to intravascular defibrination. By traumatizing the placentas of several pregnant rabbits at laparotomy similar lesions were produced.

Schneider believed that the defibrination in human beings was achieved by an "auto-injection" of thromboplastic material derived from the placental decidua or trophoblast, into the maternal circulation at the time of premature separation of the placenta.

Amniotic Fluid Embolization.—

Actually, from the clinical and pathological standpoint, the cases that most nearly resemble the experimental animals of Schneider are those of amniotic fluid embolization as exemplified by R. C. (A-40-62). These patients exhibit shock, hemorrhage, and afibrinogenemia. Although thrombi are rarely found in these cases, when they are they occur only in the lungs and except for the fact that they contain squamous cells and occasionally hair shafts, they resemble the thrombi depicted by Schneider. These are quite different from the acellular fibrin thrombi seen in the other cases in this series inasmuch as they contain leukocytes and red blood cells trapped between fibrin strands.

The sudden release of relatively large amounts of amniotic fluid containing thromboplastic material (Weiner, Reid, and Roby[26]) into the venous circulation at the time of a tumultuous labor would seem to explain the appearance of thrombi in the lungs and not elsewhere and would account also for the afibrinogenemia and severe hemorrhage which occur in these patients.

Similarity to the Generalized Shwartzman Phenomenon

While it is indeed likely that the mechanism described by Schneider may be at the root of some maternal deaths (those due to amniotic fluid embolization and possibly others), when one compares the pathologic findings in maternal autopsies in eclampsia, premature separations of the placenta, toxemia with trauma, etc., one finds certain differences. Simply stated, the major difference lies in the fact that the thrombi in human beings seem to lie for the most part on the side of the greater circulation rather than on the lesser circulation side. Hepatic arterioles, splenic arterioles, renal arterioles and capillaries, pituitary arterioles, and arterioles of the gastrointestinal tract are

found to be thrombosed. This is in contrast to the animal experiments when thromboplastin was injected intravenously, where they were found mainly in the pulmonary circulation, and only rarely in the brain.

From the pathologic standpoint a more ready, almost identical comparison can be made between the observation in the human autopsy material and the pathologic changes in animals subjected to the generalized Shwartzman reaction.

According to Thomas,[24] the cardinal pathologic feature of this phenomenon in experimental animals is bilateral cortical necrosis of the kidneys. The renal lesion is the key to this reaction and the basis for the renal lesion may be found in the glomeruli. These show the earliest changes in the development of the reaction, consisting of occlusion of the glomerular capillaries by dense masses of "homogeneous eosinophilic material." This lesion has been observed within a few hours after the provocation of the generalized Shwartzman reaction and occurs in all the kidneys which develop cortical necrosis. It offers a possible explanation for the location of necrosis within the cortex. The renal lesion shown in Fig. 1 in the patient with toxemia and a hydatidiform mole is identical with the lesion depicted by Thomas in the rabbit.

In addition, gross hemorrhages occur in the lungs, spleen, liver, lymph nodes, and gastrointestinal tracts of these animals.

Using bacterial filtrates as the toxic agent, Gratia and Linz[5] produced death associated with hemorrhages in rabbits. They injected 5 c.c. of *B. coli* active filtrate intravenously into 4 rabbits. Two received 1 c.c. of the filtrate intravenously 24 hours later. Two received 4 injections of 1 c.c. filtrate diluted 1:1,000, 1:100, and 1:10 intravenously. On the day following the completion of the experiment, one of the rabbits of the first group and 2 of the second group died. Postmortem examination showed blood in the peritoneal cavity, hemorrhages in the intestines, multiple petechiae in the kidneys, hemorrhages in the lungs, lymph nodes, thymus, and bone marrow. Apparently no histologic examination was done.

Apitz[1] in similar experiments using agar washings of *B. typhosus* and Meningococcus toxin produced similar results. The reaction in his experience was characterized by three events: (a) death within 48 hours, (b) signs of a hemorrhagic diathesis, and (c) characteristic kidney lesions of hemorrhage and necrosis. Hemorrhages were also found in the thymus, lungs, peri- and endocardium, mucosa and serosa of the gastrointestinal tract, and mesenteric lymph nodes.

The picture of the glomerular capillary thrombi produced by Thomas[24] by the injections of Meningococcus toxin are identical with those of the human kidney lesions presented in this report.

Because of this striking similarity between the pathologic changes seen in these animals and the changes in the previously described catastrophies of pregnancy, it is suggested that these conditions have a closely related etiological background.

The generalized Shwartzman phenomenon is the systemic counterpart of the Shwartzman reaction in the skin. Instead of giving a "preparing" dose

of toxin intracutaneously and the second "provoking" dose of toxin intravenously, both are given intravenously. Stated simply, the first injection brings about preparation of internal tissues which are accessible only via the circulating blood, and the second injection "fires" the Shwartzman reaction in many organs instead of in a single skin site. The toxins capable of producing the reaction are varied. Among them are Shear's polysaccharide toxin derived from *Serratia marcescens* and meningococcal endotoxin.

The phenomenon has never been observed to occur following a single injection of toxin except in two conditions. The first of these is pregnancy. Apitz[1] has observed bilateral cortical necrosis of the kidneys after a single intravenous injection of meningococcal toxin in pregnant rabbits. The second condition is produced by treatment of rabbits with large doses of cortisone (Thomas[24]). Following cortisone treatment only one intravenous dose of toxin is necessary to elicit the reaction. Apitz[1] explored several problems in relation to the development of the local and generalized Shwartzman reactions. Agar washings of *B. typhosus* and Meningococci were used as injection material. The culture fluid was centrifuged, concentrated in vacuo, and dialyzed against running water. The filtrates were checked for toxicity by observing their lethal effects with one intravenous injection and these animals served as controls. None of the changes characteristic of the Shwartzman phenomenon were found in these animals at autopsy.

He read the local reaction 5 hours after the injection. A characteristic reaction was a dark-bluish appearance with a sharply defined margin and this resulted in necrosis. Weak reactions were observed in some animals and consisted of a light red color occurring in patches which disappeared after 24 to 48 hours and did not develop necrosis.

In his first experiment it was established that more than 0.001 c.c. of toxin per kilogram was needed in the first injection to produce the generalized reaction.

In the second experiment he produced the localized reaction and then the generalized reaction in the same animal by intracutaneous injection on the first day and intravenous injection on the second and third days. From this he learned that when the weak or doubtful local reaction was obtained this was only irregularly followed by a general reaction. On the other hand, if a clear-cut local hemorrhage appeared, it was always followed by a typical general reaction. He also found that a considerably higher dose is required for intravenous preparation in case a prepared skin area with a developing hemorrhage was present. It is of interest also that if the last intravenous injection did not induce local hemorrhage, a renewed intravenous treatment would not harm the animal.

In these animal experiments it was noted that kidney damage could not be recognized until 12 hours had elapsed after the last injection and that, if necrosis developed at all, it made its appearance 24 hours after the last injection. The hemorrhagic diathesis develops more quickly. As early as 3 hours after the last injection, extensive hemorrhage may appear. When the time interval between intravenous injections was varied, reactions were regu-

larly found with intervals of 3½ to 7 hours, but if the interval exceeded 48 hours they occurred in only 1 out of 4 animals. No general Shwartzman reactions were produced in guinea pigs, rats, or mice although the filtrate that was employed exerted a regular lethal action in rats and mice when one large dose was injected intravenously.

Neither the mechanism of the fibrin deposition in the generalized Shwartzman reaction nor the mode of development of hemorrhage and necrosis in the local Shwartzman reaction are known.[18]

There are several features which suggest that the Shwartzman phenomenon is a nonspecific response on the part of the organism and is not simply an antigen-antibody reaction in the usual sense. One may produce the reaction by using a toxin from one organism in the first injection and from another organism in the second injection. Indeed, in the localized reaction at least, the second injection may be a material not only unrelated to the material of the first injection but may be a substance not generally considered antigenic at all, such as kaolin, starch, agar, or glycogen (Stetson[20]). Furthermore, that only one intravenous injection is needed in the pregnant animal or cortisone-treated animal would seem to remove it from the category of an antigen-antibody response.

It seems quite likely that the cases of pneumonia and septicemia included in this report are the human counterparts of the experiments of Apitz[1] in experimental animals. Pregnancy obviated the necessity of a "double injection" in these patients and the toxic material may have been derived from the bacteria which produced the infections.

In the attempt to explain the reactions in the other maternal deaths, particularly of the toxemic and eclamptic patients in the absence of infections, some other source of a toxin must be sought. In this regard it is of considerable interest that the Smiths[19] have demonstrated a toxic material in the decidua of pregnancy in patients with toxemia. This toxin is lethal to immature rats when subcutaneously injected and appears to be similar to the lethal substance obtainable from menstrual blood. The endometrial debris of menstrual blood appears to be the source of this toxin. It is quite labile and is destroyed by prolonged dialysis, by hydrogen ion concentrations above 7 or below 6, by temperatures above 45° C., and by organic solvents that precipitate protein. The toxin will not pass through a Seitz filter which differentiates it from many bacterial toxins. However, one thing which this toxin has in common with the Shwartzman active material (Apitz[1]) derived from bacteria is that they both may be derived from products of catabolism. Also, they are both very labile substances.

It is suggested that such a product of catabolism in the decidua or placenta is responsible for the activation of the generalized Shwartzman reaction in certain pregnant individuals.

Conclusions

It is suggested that toxic material suddenly released into the maternal blood stream is responsible for the deposition of fibrin, the hemorrhages and

necroses, and the acute clinical symptoms of shock, anuria, and hemorrhage in toxemic patients with premature separation of the placenta and in eclamptic patients, and that these conditions are manifestations of the generalized Shwartzman phenomenon in human beings.

It is further postulated that a regular course of events may take place in these patients. The pregnancy "prepares" the blood vessels and the premature separation of the placenta releases "toxin" from the necrotic decidua in the circulation which amounts to the "provoking" dose in the Shwartzman phenomenon. This results in intravascular fibrin deposition in many organs. Hemorrhage may follow and shock is superimposed if the hemorrhage is severe. Shock results in the release of fibrinolysin which may lyse many or all of the fibrin thrombi. The patient may die suddenly, may develop pituitary necrosis, bilateral renal cortical necrosis, or extensive liver damage and succumb to these disasters. Some patients may survive in spite of severe pathologic changes in the pituitary, kidney, or liver, and some may survive unscathed.

Summary

Intravascular fibrin deposition in arterioles and capillaries throughout the body is responsible for the necrosis and hemorrhage seen in eclampsia, bilateral renal cortical necrosis, and pituitary necrosis associated with pregnancy. These cases are often accompanied by severe shock, hemorrhage, and anuria. Fibrinogenopenia and fibrinolysins develop in this group of patients. It is suggested that the mechanism behind the fibrin deposition is similar to that in the generalized Shwartzman reaction. In some cases the source of "toxin" may be a bacterial infection. In some cases, particularly those associated with toxemia of pregnancy, the "toxin" may be similar to the "menstrual toxin" described by the Smiths.

We wish to express our appreciation to Miss Mary Cronan and Mrs. Estelle Freeman for help in preparing the manuscript and to Leo Goodman for the photomicrographs.

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THE IMMEDIATE EFFECTS OF PROLONGED LABOR WITH FORCEPS DELIVERY, PRECIPITATE LABOR WITH SPONTANEOUS DELIVERY, AND NATURAL LABOR WITH SPONTANEOUS DELIVERY ON THE CHILD*

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TWO papers have been prepared which deal with the effects of labor on the child. The first is concerned with the immediate, the second with the remote results, the so-called late neurological sequelae. A study of these two related subjects has been made on a common population in order to understand more fully the problem of permanent birth injury.

The differences in the immediate effects of prolonged labor with forceps delivery, precipitate labor with spontaneous delivery, and natural labor with spontaneous delivery on the child are compared. These differences are reflected in the incidence of apnea, intrapartum stillbirth, and neonatal death. In order to reduce the number of variables, only mature infants born in cephalic presentation are considered. A mature infant weighs 2,500 grams or over.

The exact point at which labor starts is difficult to determine. This is particularly true in prolonged labor which frequently is preceded by a prodromal stage, which lasts from hours to days and is characterized by painful uterine contractions. This prodromal stage is not labor. Labor starts with the beginning of dilatation of the cervix. A prolonged labor lasts twenty-four hours or longer. A precipitate labor is two hours long or less. Precipitate labor is not to be confused with unattended birth. An unattended birth may be a precipitate labor, but a precipitate labor is not necessarily an unattended birth. A natural labor lasts longer than two hours and less than twenty-four hours, with a second stage of less than an hour and a half.

This analysis was made at the Chicago Maternity Center, and covers the pertinent births which occurred during the twelve-year period, 1934-1945. This population coincides with that from which the 135 children were chosen for the second study. The volume of deliveries was so great that the incidence of apnea in natural and precipitate labor was determined for one year only, 1938. The incidence of apnea in prolonged labor with forceps delivery was ascertained for the entire period. The results are comparable because the population and the methods used in the conduct of labor were constant.

*Presented at a meeting of the Chicago Gynecological Society, Feb. 20, 1953.

The incidence of intrapartum fetal death and neonatal death was determined for the entire twelve-year period. A clinicopathological analysis of each infant death was made from documented birth records and autopsy protocols.

Autopsy protocols were available on 83 per cent of the deaths. Fifty per cent of the autopsies were done at Chicago Lying-in Hospital, the remainder at Cook County, Children's Memorial, Provident, and Michael Reese Hospitals. Five of the 18 babies lost in the prolonged labor forceps group were delivered by craniotomy following failed forceps. The intracranial relationship was unknown in these 5 children.

Statistical Evaluation[1]

The data were subjected to three methods of statistical evaluation, in appropriate places. Chi-square* tested the reality of association. The 95 per cent Confidence Interval† determined the degree of confidence which could be placed on the observed values. Covariance was used to control for differences in chronological age, in the second paper.

Special attention is given the problem of cerebral hemorrhage. It is a major factor in the production of infant death, and is considered responsible for a larger or smaller number of mentally defective individuals among those who survive.

The Literature

Any circumstance which affects the baby adversely during labor may be considered a cause of birth injury. We are accustomed to differentiate trauma and anoxia. Trauma is the result of mechanical force. Although the baby's head is architecturally well constructed to resist the counterforces of labor, and even instrumentation, intracranial injury has been observed following every type of delivery. In case of death, lacerations of the supporting structures and vessels of the brain may be found.

The effects of anoxia on the child are more difficult to understand than those of mechanical trauma. Anoxia exists if the available oxygen falls below the physiological needs of the organism.[2] Often this is a purely functional disorder and in case of death no anatomical cause is demonstrable. Under other conditions the organism makes a physiological tissue response. All the tissues of the body respond in the same way, but to a variable degree, to oxygen want. Edema, hyperemia, and hemorrhage appear in the order stated. Up to a point these changes are reversible. If oxygen is supplied no permanent damage results; if not, death follows. As to whether or not irreversible changes occur short of death is debatable.

*Chi-square analysis is a method of determining the statistical significance of comparative data. The results of such analysis are displayed by an equation. This tells the probability of chance occurrence of the ratio under consideration. If a certain ratio occurs by chance once in ten times the representative equation is: $P = 0.10$; if it occurs once in one hundred times; $P = 0.01$ tells the story; and once in one thousand times is represented by the equation $P = 0.001$. Once in ten times is considered merely indicative that a ratio might be important; once in one hundred times is highly significant; and once in one thousand times is irrefutable. Of course, the number of cases in a study is of importance. The greater the number, the greater weight can be placed upon the conclusions.

†The 95 per cent Confidence Interval is a statistical method used to determine the degree of confidence which may be placed on an observed value for any population characteristic. The observed value determined on a sample differs from the true value for the population as a whole. The latter is expressed not as a single figure, but as two figures which, 95 per cent of the time, define the range within which the true value lies. If this range is too great, confidence cannot be placed on the observed value.

Investigators agree that the infant mortality rate is in direct proportion to the degree of trauma and anoxia experienced at birth. Potter,[2] 1952, at the Chicago Lying-in Hospital, observed a reduction in the incidence of cerebral hemorrhage at autopsy on infants, from 14 per cent (1932-1945) to 3 per cent (1947-1949), and stated that, as the judgment and technical skill of the obstetrician increase, infant deaths from cerebral hemorrhage or other birth injuries decrease.

Clifford,[3] in 1948, found that 60 per cent of infant deaths were due to anoxia and concluded that this percentage could be materially reduced by the prevention of accumulative anoxia. The Boston Lying-in Hospital reduced the infant mortality for babies who weighed 5 pounds or less, delivered by cesarean section, from 54 per cent to 16.5 per cent, by the simple expedient of limiting the amount of general anesthesia used at operation.

Two types of cerebral hemorrhage are described, traumatic and anoxic.

Traumatic Cerebral Hemorrhage.—

If the supporting structure and vessels of the brain are subjected to too much strain and stress, lacerations resulting in cerebral hemorrhage occur. Usually, they are incompatible with life. The hemorrhages are relatively large, and disruption of vessels can be demonstrated at autopsy. The most ordinary lacerations are of the falx, tentorium cerebri, and the vein of Galen, which lies at the base of the brain. Intraventricular hemorrhages rarely occur in the mature infant; meningeal hemorrhages do occur.

Other factors besides trauma are concerned in the formation of traumatic cerebral hemorrhage. Anoxia is both a predisposing and contributing cause.[4, 5, 6]

Schwartz,[7] in 1927, believed that under certain circumstances the subnormal pressure effect exerted on the head, incident to rupture of the bag of waters, produced intracranial injury. Ehrenfest,[5] in 1922, found syphilis a predisposing agent.

Residua of Traumatic Cerebral Hemorrhage.—

A few meningeal hemorrhages are compatible with life, and lead to the formation of subdural hematomas. Elwidge and Jackson,[8] 1949, stated that this condition is frequently not diagnosed following delivery. If it is not treated it leads to marked mental deterioration. Of the 140 cases reported in the literature, 14, or 10 per cent, were due to birth injury.

Penfield,[9] 1940, demonstrated adherent meninges and microgyri at craniotomy on patients who suffered focal epilepsy. He considered these residua of birth injury.

Anoxic Cerebral Hemorrhage.—

Anoxic cerebral hemorrhage has been described by Potter,[2] Gruenwald,[6] 1950, and MacGregor,[10] 1946.

Although anoxic cerebral hemorrhage is attributed to a lack of oxygen, under certain circumstances it is not unreasonable to suppose that trauma,

also, contributes to its formation (Zuelzer,[11] 1948, Gruenwald[6]). In contradistinction to traumatic cerebral hemorrhage, there is no demonstrable disruption of major blood vessels. The hemorrhages are small due to oozing of the blood through the capillary walls. Circumscribed petechiae may occur in showers throughout the meninges and brain substance. Potter[2] notes that this is a characteristic finding in abruptio placentae. In other cases the cerebrum may be covered with a film of blood, or diffuse sheets of blood may occur in the meninges. Subarachnoid hemorrhages are considered due to anoxia. Anoxic hemorrhages in themselves are not a cause of death, but considered a terminal manifestation of shock or of a failing cardiovascular system.[6]

Residua of Anoxic Cerebral Hemorrhage.—

The controversy regarding whether or not permanent brain damage results from residua of anoxic hemorrhage in those who survive is set forth fully in the second paper. MacGregor[16] states that this type of hemorrhage rarely leads to residua. She presents one exception. A baby developed marked hydrocephalus during the first year of life. He died and came to autopsy. Subarachnoid hemorrhage incurred at birth was found to be the cause of the hydrocephalus.

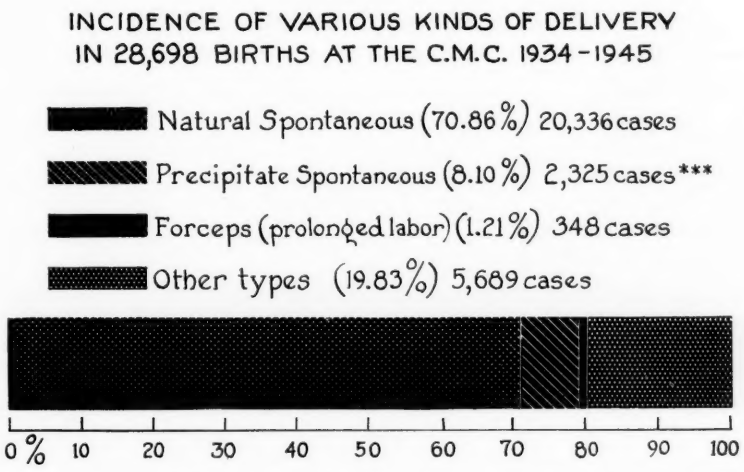
INCIDENCE OF VARIOUS KINDS OF DELIVERY
IN 28,698 BIRTHS AT THE C.M.C. 1934-1945
Natural Spontaneous (70.86%) 20,336 cases
Precipitate Spontaneous (8.10%) 2,325 cases***
Forceps (prolonged labor) (1.21%) 348 cases
Other types (19.83%) 5,689 cases
0% 10 20 30 40 50 60 70 80 90 100

Fig. 1.—Shows the distribution of deliveries during the years 1934-1945.

Hughes,[12] 1948, at Memphis, has done much interesting work with encephalograms on the mature newborn infant. Prominent dysrhythmia of the tracings gave evidence of lack of functional organization of the cerebrum. The brain waves were immature. However, he has established what he considers an average pattern. Eight encephalograms on babies born with clinically demonstrable injury showed marked variations from the normal. Some of these children were followed for several months. Although, clinically, they recovered completely from the birth injury, the encephalograms remained abnormal. One died and autopsy revealed extensive bilateral subarachnoid hemorrhage.

Statistical Observations on Apnea, Intrapartum Fetal Death, and Neonatal Death

In the twelve-year period, 1934-1945, 28,698 infants were born at the Chicago maternity Center. Twenty-three thousand nine, or 80 per cent, were mature infants born in cephalic presentation, by one of the three types of labor considered in this study. Of the total births, 20,336, or 71 per cent, were natural labors and spontaneous deliveries, 2,325, or 8 per cent, were precipitate labors and spontaneous deliveries,* and 348, or 1.21 per cent, prolonged labors with forceps deliveries. The remainder, 5,689 births, or 20 per cent, were either of premature infants, or of mature infants born in other than cephalic presentation, or by prolonged labor with spontaneous delivery (Fig. 1). The last 20 per cent fall outside the scope of this paper.

The Incidence of Apnea

Fig. 2 presents the incidence of apnea, and Table I the degree of apnea in the labors studied.

TABLE I. DEGREE OF APNEA IN THE THREE DIFFERENT TYPES OF LABOR AND DELIVERY, CHICAGO MATERNITY CENTER

TYPE OF LABOR AND DELIVERY	PRECIPITATE SPONTANEOUS	NATURAL SPONTANEOUS		PROLONGED FORCEPS SEDATION AND NERVE BLOCK ANESTHESIA			
TYPE OF PAIN RELIEF	0	0	SEDATION	LOW	MID	HIGH	TOTAL
No. births considered	253	2,081	140	194	137	17	348
No. with apnea	14	86	12	31	44	8	83
Degree:							
Mild	6	31	6	8	6	1	15
Moderate	6	49	6	20	26	3	49
Severe	2	6	0	3	12	4	19

A baby that does not breathe within thirty seconds of birth is apneic. Flagg's,[13] 1931, classification is used. In mild apnea, respiration is delayed a short time, the body tone is good, and all of the reflexes are present. In moderate apnea, the body tone is poor, the superficial reflexes are absent, and the baby may gasp occasionally. In severe apnea the baby appears as if dead. He may be livid or pallid. All of the reflexes are absent and the body is flaccid. Cardiac embarrassment is present, the heartbeat is slow and irregular.

No anesthesia was used in the cases of natural and precipitate labor. Ninety-seven per cent of the operative deliveries were performed under parasacral or pudendal block, and 3 per cent under ether anesthesia. Sedation was given in 6.3 per cent of the natural labors, and not at all in the precipitate labors. This sedation usually consisted of morphine, 16 mg., or Demerol, 100 mg., given once, supposedly not within four hours of delivery. In prolonged

*Estimated from samplings of five groups chosen at random from deliveries which occurred from 1934 to 1945. Each group was made up of 500 consecutive deliveries of mature infants born in cephalic presentation.

labor cases, morphine or Demerol was also used. In 9.17 per cent it was repeated once (in 2 cases twice). Ether, quinine, and oil were given by rectum in 7.47 per cent of the forceps deliveries.

The incidence of apnea among natural births, where no sedation was used, was 4.13 per cent. In a comparable group of cases the incidence of apnea at Boston Lying-in Hospital[14] was found to be 1.9 per cent, 1940, at Harper Hospital,[15] in Detroit, 5.4 per cent, 1939. In our study, where sedation was used in natural labor, the percentage of apneic babies was 8.57. This percentage is somewhat larger than in cases where no sedation was used (P = 0.01). Cole,[16] 1941, found that in natural labor 25 per cent of babies, born of mothers who were adequately sedated, suffered some degree of apnea. These women received larger doses of medication than those on the service of the Center.

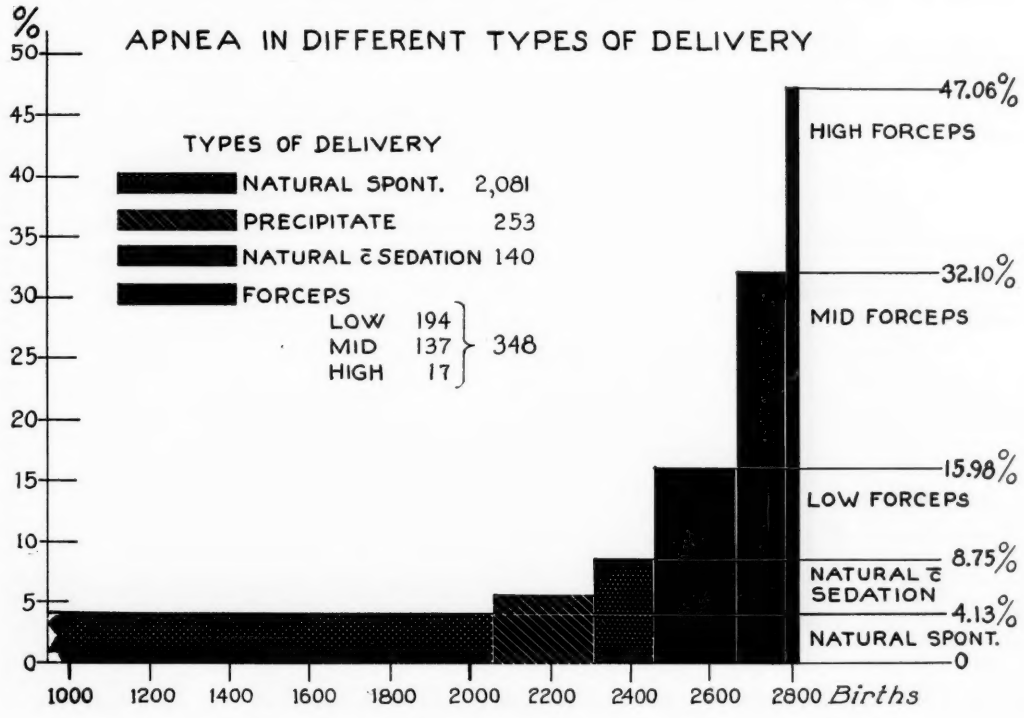

Fig. 2.—Shows the incidence of apnea in the 3 groups.

The incidence of apnea in the precipitate group, 5.53 per cent, was not significantly larger than in the natural labor group. McPhail,[17] 1941, states, but gives no proof, that the incidence of apnea in precipitate labor is much higher than in natural labor.

The percentage of apnea was higher after prolonged labor with low forceps delivery, 15.98 per cent, than after natural labor with sedation, 8.5 per cent; and was appreciably higher after midforceps, 32.12 per cent, and high forceps, 47.06 per cent, than after low forceps delivery (P = 0.004). Although the number of high forceps deliveries was too small to warrant a statistical conclusion, critical obstetrical opinion would agree with these observa-

tions. A consideration of the data leads to the conclusion that the percentage of apnea is directly in proportion to the degree of trauma experienced by the baby, P = 0.004, and that transplacental narcosis from sedation is also a factor in its production, P = 0.04.

Lund,[18] 1942, analyzed the incidence of apnea in various operative procedures performed under general anesthesia. He feels that general anesthesia does not add materially to the incidence or degree of apnea in the baby, and that trauma is the chief factor in its production. Apnea rates quoted by him vary from 25 per cent to 45 per cent.

The Incidence of Intrapartum Fetal Death and Neonatal Death

An intrapartum fetal death is the death of a baby during labor. A neonatal death is one that occurs during the first month of life.

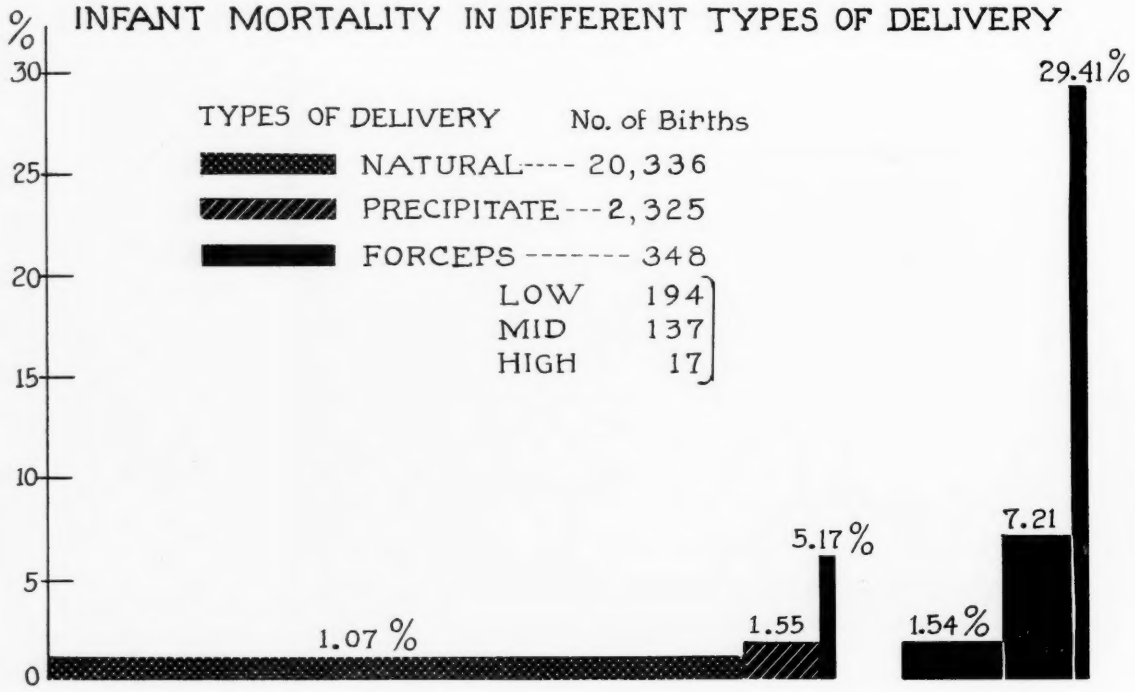

Fig. 3.—Shows the total stillbirth and neonatal mortality for all 3 groups. The graph on the right (scaled 15 times greater) shows the combined fetal loss for the different types of forceps.

Fig. 3 displays the combined incidence of intrapartum fetal deaths and neonatal deaths for natural and precipitate labor with spontaneous delivery, and for prolonged labor with forceps delivery. These are 1.5 times greater for precipitate labor with spontaneous delivery than for natural labor with spontaneous delivery (P = 0.04), and 4.83 times greater for prolonged labor with forceps delivery than for natural labor. The percentage of babies lost in the low forceps group equals the percentage lost in the precipitate group. Four and seven-tenths times more were lost by midforceps than by low forceps, and 19 times more by high forceps (P = 0.00001).

A low forceps operation is an extraction from below a plus 2 station; a midforceps, from zero to plus 2 station, and a high forceps, from above zero station.

Fig. 4 shows the incidence of the various causes of infant death, as determined at autopsy on 222 infants who were stillborn or who died in the neonatal period. These are divided into four groups: birth injury, abnormal pulmonary ventilation, anoxia, and other causes. The birth injury category includes deaths from cerebral hemorrhage, skull fracture, ruptured liver, and ruptured adrenal. Abnormal pulmonary ventilation (Potter's[2] term) includes deaths, exclusive of those from anoxia, where no specific pathology was present outside the lung. In the anoxic group are placed children known to have died from compression of the cord, abruptio placentae, placenta previa, and rupture of the uterus. Other causes of death include abnormalities of development, infections, and erythroblastosis.

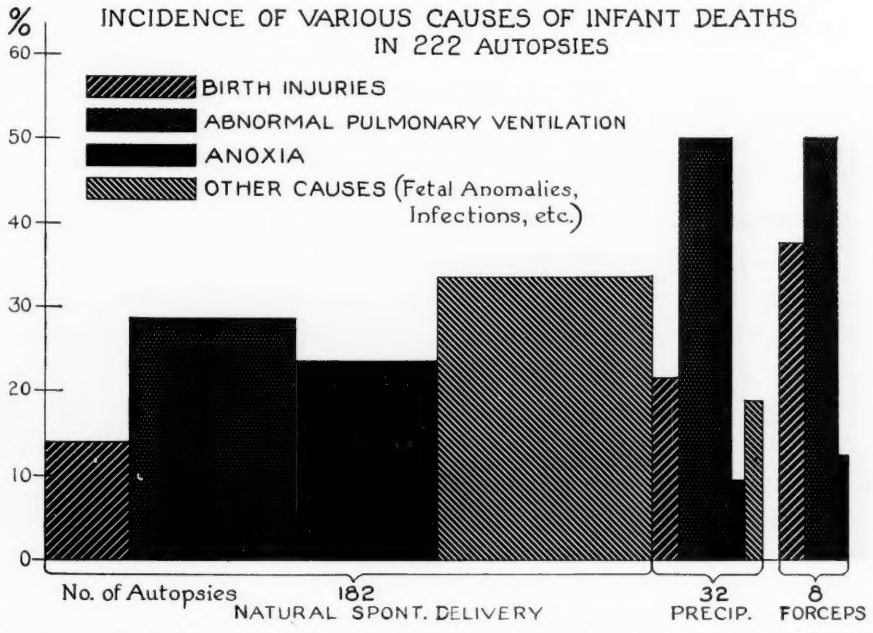

Fig. 4.—Shows the incidence of the various causes of death found at autopsy in the 3 groups.

A comparison of the observed values for the causes of infant death shows very little difference of statistical significance in the three groups of labor. There is one possible exception. Abnormal pulmonary ventilation occurred twice as frequently following precipitate labor with spontaneous delivery as following natural labor with spontaneous delivery. This is significant at $P = 0.03$.

Table II displays the observed incidence of traumatic and anoxic cerebral hemorrhage.

The three types of labor do not show any statistically significant difference in regard to the incidence of either traumatic or anoxic cerebral hemorrhage. The number of cases observed in the prolonged labor and forceps group is too

small to warrant any conclusion regarding the incidence of cerebral hemorrhage following this type of labor. However, other groups of observers, Bundesen, Potter, and associates[19] 1951, have reported figures on a large number of autopsied cases. They find traumatic cerebral hemorrhage is much higher following low forceps, 22.4 per cent, and following mid- and high forceps deliveries, 54.7 per cent, than following natural births, 13.9 per cent.

TABLE II. THE OBSERVED INCIDENCE OF TRAUMATIC AND ANOXIC CEREBRAL HEMORRHAGE IN 222 AUTOPSIES, CHICAGO MATERNITY CENTER, 1934-1945

TYPE OF LABOR	NATURAL		PRECIPITATE		PROLONGED	
Delivery	Spontaneous		Spontaneous		Forceps	
No of births	20,336		2,325		348	
Stillbirths and neonatal deaths	218 1.07%		36 1.55%		18 5.17%	
Autopsy	182		32		8	
	TRAUMATIC INTRACRANIAL HEMORRHAGE	ANOXIC INTRACRANIAL HEMORRHAGE	TRAUMATIC INTRACRANIAL HEMORRHAGE	ANOXIC INTRACRANIAL HEMORRHAGE	TRAUMATIC INTRACRANIAL HEMORRHAGE	ANOXIC INTRACRANIAL HEMORRHAGE
Observed at autopsy	18	10	6	1	2	1
Observed (%)	9.89	5.49	18.75	3.12	25.00	12.50
95% confidence interval (per cent)	6.33-15.12	3.00-9.84	9.89-35.40	0.55-15.84	8.5-65.0	21.0-52.5

Traumatic and Anoxic Cerebral Hemorrhage in Natural Labor

A study was made of the birth records of 18 children, in whom traumatic cerebral hemorrhage, and of 10 children, in whom anoxic cerebral hemorrhage was found at autopsy following natural labor and spontaneous delivery. In 8 of the 18 cases of traumatic hemorrhage, major anoxic conditions were present. These included abruptio placentae, prolapsed cord, tumultuous labor, and excessive compression of the chest, in the postmature infant. In 7 of the 10 cases of anoxic cerebral hemorrhage, similar anoxic factors were present. There was one exception—tumultuous labor was not noted in the anoxic cerebral hemorrhage group. Excessively large babies, small babies, toxemia, and diabetes were common to each group.

It is difficult to evaluate the element of trauma in the production of these hemorrhages in natural labor. The cephalopelvic adaptation was good, with the exception of one case in which the baby was delivered from the occipitosacral position. Tumultuous labor undoubtedly gives rise to trauma as well as to anoxia, and the head of an excessively large infant suffers more compression than that of the average-sized baby.

Traumatic and Anoxic Cerebral Hemorrhage Following Precipitate Labor

A similar analysis of the 6 cases of traumatic cerebral hemorrhage known to have occurred in the precipitate group shows that all were unattended births. One baby was removed from the toilet bowl ten minutes after birth, one was born following a single pain, and in another case the labor lasted only fifteen minutes. There was only one anoxic hemorrhage in this group.

Traumatic and Anoxic Cerebral Hemorrhage Following Prolonged Labor and Forceps Delivery

Traumatic and anoxic cerebral hemorrhages in the prolonged labor with forceps delivery group are not discussed at length. The intracranial relationship was unknown in 10 of the 18 cases. In the 2 cases of traumatic and the 1 case of anoxic hemorrhage which occurred, poor cephalopelvic adaptation, stagnant anoxia, and intrapartum sepsis played a role.

Combined Incidence of Traumatic and Anoxic Cerebral Hemorrhage

Table III presents the observed and computed incidence of traumatic and anoxic cerebral hemorrhage, with the ratio of occurrence, in the 23,009 infants.

TABLE III. TOTAL OBSERVED AND COMPUTED TRAUMATIC AND ANOXIC CEREBRAL HEMORRHAGE WITH RATIO OF OCCURRENCE IN 23,009 BIRTHS AT THE CHICAGO MATERNITY CENTER, 1934-1945

Number of births			23,009
Stillbirths and neonatal deaths			272
Autopsy			222
	TRAUMATIC INTRACRANIAL HEMORRHAGE	ANOXIC INTRACRANIAL HEMORRHAGE	TOTAL INTRACRANIAL HEMORRHAGE
Observed at autopsy	26	12	38
Observed (%)	11.71	5.41	17.12
95% Confidence interval (per cent)	8.10-16.64	3.11-9.23	12.71-22.5
Computed No.	31.8558	14.703	46.558
Per cent of total births	0.14	0.06	1:494.2 ratio

Cerebral hemorrhage, either traumatic or anoxic, occurred in 17 per cent of the total autopsies. It is difficult to believe that cerebral hemorrhage occurs any more frequently in those who survive than in those who die. Therefore, it is hard for us to accept Aschoff's statement, as quoted by Brouwer, that hemorrhage in the pia, arachnoid, and the central nervous system may occur in almost every birth. The estimated ratio of cerebral hemorrhage (traumatic and anoxic) was 1:494 deliveries (natural, precipitate, and prolonged).

Conclusions

1. The incidence of apnea neonatorum is directly in proportion to the degree of trauma suffered by the baby. It is lowest in natural labor and highest in prolonged labor followed by forceps delivery. The more difficult the operative procedure, the greater the incidence and degree of apnea. There is no significant difference in the incidence of apnea following natural and precipitate labor. The use of sedation, within pharmacological limits, increases the incidence of apnea somewhat, but to a less degree than trauma increases it.

2. The incidence of stillbirth and neonatal death is also directly in proportion to the degree of trauma and anoxia the child suffers. It is lowest following natural labor, appreciably higher following precipitate labor, and highest following prolonged labor with forceps delivery.

3. There is an indication that abnormal pulmonary ventilation is higher following precipitate labor than following natural labor with spontaneous delivery.

4. There was no statistically significant difference in the incidence of either traumatic or anoxic cerebral hemorrhage, as determined at autopsy, in the three types of labor. This observation is definitely inconclusive. Not sufficient data were available in the precipitate and in the prolonged labor groups.

5. Traumatic cerebral hemorrhage is exceedingly rare following uncomplicated natural labor with spontaneous delivery.

6. Anoxia and trauma are so intimately associated in the production of traumatic cerebral hemorrhage that many times it is impossible to separate one from the other as a causative factor.

References

(For references, see page 565 following second paper.)

Discussion

(For discussion, see page 566.)

THE REMOTE EFFECTS OF PROLONGED LABOR WITH FORCEPS DELIVERY, PRECIPITATE LABOR WITH SPONTANEOUS DELIVERY, AND NATURAL LABOR WITH SPONTANEOUS DELIVERY ON THE CHILD*

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THE problem is to determine whether there are any differences in the effect of prolonged labor with forceps delivery, precipitate labor with spontaneous delivery, and natural labor with spontaneous delivery on the development of the child. Only children born as mature infants in cephalic presentation are considered.

Children between the ages of 5 and 15 years were selected and were examined and tested for variation in their physical and mental developments. The children were chosen from documented birth records available at the Chicago Maternity Center. As random a selection as possible was made. This will be discussed later. One hundred thirty-five were selected and divided into three groups. Forty-seven were in the prolonged labor with forceps delivery, 45 in the precipitate labor with spontaneous delivery, and 43 in the natural labor with spontaneous delivery groups. For purposes of statistical analysis of the data obtained from the psychological and pediatric examinations and tests, the entire group was reduced from 135 to 120, with 20 males and 20 females in each of the three groups. Ten of the males and 10 of the females in each category were Negroes, and 10 males and 10 females were white.

The analysis of the neurological material did not require the same treatment and data from all the 135 children were retained.

The obstetrician who undertakes such a study is handicapped by his short span of observation. He is familiar with the growth of the fetus in the uterus and the immediate effects of labor on the child. He is less familiar with the possible remote results, the so-called neurological sequelae. Those are usually brought to his attention, accidentally, by the mother who seeks advice regarding consultation with a neurologist or psychiatrist, because of abnormalities in the growth and behavior pattern of the developing offspring.

The physician who observes a child throughout the entire period of growth, and who is familiar with methods of physical and psychological examinations and diagnostic tests may be unable to interpret the birth record lucidly. This study has been a cooperative undertaking at the Northwestern

*Presented at a meeting of the Chicago Gynecological Society, Feb. 20, 1953.

University Medical School, with Dr. Vida Wentz, in pediatrics, Dr. Meyer Brown and Dr. G. K. Yacorzynski, in the department of nervous and mental diseases, Dr. Harry B. W. Benaron and Dr. Beatrice E. Tucker, in obstetrics, participating.

General Approach

In the past there have been two main approaches to this problem. In the first, a large group of mentally defective people, usually the inmates of an asylum, were chosen and an attempt made to ascertain the birth history. Correlation was then made between the occurrence of birth injury and later developmental anomalies. There is such a wide discrepancy in the results of different investigators that we are skeptical of the accuracy of such a method. For example: Schreiber,[20] 1940, a neurosurgeon, in Detroit, found that 70 per cent of 500 mentally defective inmates of an asylum suffered apnea at birth and ascribed their neurological lesions to that circumstance, while Penrose,[21] 1949, professor of genetics at the University of London, found less than 1 per cent of neurological lesions, in a similar group of 1,280 mentally defective patients, attributable to apnea or injury at birth.

The second method starts with a documented birth record and later attempts to locate the child and evaluate the development. Many children cannot be found and the number studied is small. However, the papers of Darke,[22] 1944, and Preston,[23] 1945, are impressive. Darke presents 49 case reports on deeply apneic babies. These children were located and intelligence tests made. Siblings and parents were used as controls. He concludes that severely apneic newborn infants, with no evidence of injury at birth or following, are significantly retarded in mental development. He combed two large obstetrical services to find the 49 children, and there is no doubt in the reader's mind that they suffered from severe anoxia at birth.

Preston presents continuous developmental histories of 2 children who suffered severe apnea at birth. They showed marked abnormalities in their behavior patterns.

We have chosen the second method of approach.

Literature

A common etiology, that of birth injury, may be responsible for symptoms which appear immediately after birth, or which follow at a later period. The question arises, do permanent structural and functional changes occur in the central nervous system of the child who survives birth injury, due to either mechanical trauma or anoxia? The literature on this subject is controversial.

Cerebral dysplasia or spastic paralysis once, almost universally, considered to be the result of abnormal parturition, difficult labor, premature birth, and asphyxia neonatorum,[24-28] 1861-1888, is now considered, in the majority of cases, to be due to other factors, such as genetic predisposition, anomalous intrauterine development, or acquired infection,[21, 29, 30] 1897-1949.

There are two opposing views as to whether or not paranatal (prenatal, natal, and postnatal) anoxia alone can give rise to residual pathology in the central nervous system which leads to neurological sequelae.

Schreiber,[20] 1940, believes that residual lesions are produced by paranatal anoxia which are compatible with life, but are demonstrable, in case of death, in the cerebral architecture. He finds, "the commonest presenting symptom is deterioration of intellect, evidenced by character change and memory defect." Lund,[31] 1943, Courville,[32] 1944, Windle,[33] 1944, Darke,[22] 1944, and Preston,[23] 1945, support this hypothesis.

Zuelzer,[11] 1948, disagrees. He considers that the correlation of anoxia at birth with the development of later neurological lesions has no factual support and is based on inference only. He believes anoxia to be purely a concept of pathological physiology which cannot be defined in terms of anatomical pathological lesions, and states that organic lesions attributed to it are not specific and give no clue to the cause.

Repeatedly the statement occurs in the above-mentioned literature that if a neonate suffers oxygen deprivation for a period of from three to eight minutes, irreversible changes occur in the brain which, though compatible with life, lead to residual lesions in the central nervous system. This opinion is based on the assumption that the results of experiments in anoxia on the cat apply directly to the human newborn infant.

Animal experimentation shows that various species differ considerably in their ability to withstand oxygen deprivation. In general, the younger the animal, the more resistant is the nervous system to lack of oxygen.[34] According to Ford,[35] 1944, kittens show no morphological or functional changes after twelve hours of sublethal oxygen deprivation, while Weinberger,[36] 1940, and Tureen,[37] 1936, found that cats display extensive degenerative changes after a few minutes of oxygen deficiency. The cat is less resistant than is the dog,[38] the monkey,[39] or the rat.[40] These results show that one cannot generalize, from animal experimentation, what will occur in the human infant under similar conditions of anoxia.

Definite structural and functional changes take place in the adult brain after exposure to severe anoxia. Courville,[32] 1944, concluded that similar changes occur in the brain of the newborn.

Zuelzer[11] believes such a deduction is dubious. The fetus and newborn baby have a physiology peculiar to their time of life which protects them from variations in oxygen supply incident to labor and delivery, which otherwise might prove harmful.[34, 41-44] This will be considered in more detail later.

Hannes,[45] 1911, Sturma,[46] 1949, McPhail,[17] 1941, and Keith,[47] 1950, find that difficult and apneic births do not contribute to mental retardation, idiocy, or other neurological sequelae more frequently than spontaneous births.

There are similar inconsistencies in the literature regarding the importance of residual lesions from meningeal and other cerebral hemorrhages which occur at birth.

Weyhe,[48] 1889, performed 957 autopsies on children from a few days to 6 months of age. Thirteen per cent had meningeal hemorrhage. None showed any functional sign or symptom of brain damage.

Ehrenfest,[5] 1922, stated, "From a careful perusal of the literature, the definite deduction can be drawn that convincing anatomical evidence for an important or frequent causative connection of intracranial birth lesions to mental deficiency is still wanting."

However, Brouwer,[49] 1949, and others,[4, 8, 9, 41, 42, 50, 51] have performed autopsies on children who suffered birth injury, developed neurological lesions, and died later of unrelated cause. Cerebral hemorrhage was found, with alterations in the cerebral cortex which spread further than the area of local injury. Idiocy, blindness, mental retardation, epilepsy, and spastic paralysis occurred in these patients.

The literature fails to supply an answer to the question as to what may be the long-range effects on the child who survives with injury. The two opposing views on this problem are illustrated by Ford,[35] 1944, and by Gesell,[52] 1949.

Ford states, "When the diagnosis of cerebral injury is established beyond a doubt at birth the child either dies, or within a few days makes a complete recovery in most instances. Only a few children survive with definite residua." In contradiction, Gesell believes that minimal injuries at birth are more common than is ordinarily supposed, and may offset the development of the child later in life. He states: "They do not yield to ordinary methods of clinical neurology. They can only be elicited by systemic developmental examination of the infant behavior."

The Chicago Maternity Center and the Population Served

A knowledge of certain factors peculiar to the service of the Chicago Maternity Center and to the population which it serves aids in an understanding of how the deliveries were conducted and furnishes a picture of the environment from which the children sprang.

The Center is a large outpatient obstetrical clinic, which might be termed a field hospital. All of the deliveries, including difficult operative cases, are conducted in the home. Every safeguard is made available to the patient, including oxygen and blood transfusion, through the courtesy of Michael Reese blood bank.

At the present time most of the patients requiring hospital care are taken to Wesley Memorial Hospital. The Center is a teaching clinic, serving three large universities, Northwestern, Wisconsin, and Chicago Medical Schools. The multiparous women are delivered by a medical student, under the supervision of an assistant resident, the primiparous women, by an assistant resident, and the operative cases by a resident, under the supervision of an attending obstetrician. The cases are scattered throughout the entire city of Chicago. A resident with a car circulates, and one is on call constantly at the Center in case of emergency. The medical and nursing crew stays in the home with the patient throughout labor and until two hours after delivery. The postpartum nursing care is given by the Visiting Nurse Association.

The Center serves a polyglot group of people, at the present time predominantly Negro, but, during the depression, predominantly white. Its popu-

lation consists of forty-eight nationalities. Among the white patients, the Mexican, Polish, and Italian are numerically highest. Some live in rat- and vermin-infested tenement homes, under conditions of filth, squalor, and overcrowding, difficult to condone in any community. Their standard of behavior is different from that of a more privileged society. Illegitimacy has increased from 2.21 per cent in 1932, to 22.14 per cent in 1950. This requires interpretation. With the advent of Aid to Dependent Children, the incidence rose sharply. We believe this increase is more alleged than real.

The incidence of maternal syphilis is high. At the beginning of the war, in 1941, it was 7.31 per cent, in the delivered cases. It dropped to 5.14 per cent in 1943, rose to 8.15 per cent in 1944, and climbed to 10.6 per cent in 1945. Although only 5.63 per cent of the infants who came to autopsy died of syphilis, the incidence of maternal syphilis among the stillbirth and neonatal death groups (1934-1945) was 17.7 per cent ($P = 0.006$).

In spite of the fact that a dietician is available at the Center, the incidence of metabolic disorders and malnutrition runs high. Six per cent of the delivered patients whose weight was recorded weighed 200 pounds or over. Thirty-three and thirty-three one-hundredths per cent of the mothers who lost their babies after prolonged labor with forceps delivery weighed 200 pounds plus, and, of these, 4 out of 5 mothers, who were delivered by craniotomy after failed forceps, tipped the scales between 250 and 500 pounds (1934-1945).

In general, it may be said that 1 delivery in 6, or 16.7 per cent, was an unattended birth; 15 per cent of the patients had no prenatal care and were first seen in labor; 17.15 per cent were primiparas and 82.85 per cent, multiparas.

Although the Center's service and population are different from the usual obstetrical service, the techniques are standardized, and the patients are cared for in a uniform manner. The population, though varied in background, is homogeneous in its poverty and lack of socioeconomic opportunity, and lends itself to a study of this nature.

A home delivery service furnishes a particularly suitable group of cases for the study of the effects of labor alone on the child without the usual adjuvants, sedation and anesthesia. The use of these by necessity is limited. Sedation was given on indication only. In natural labor, during the time of this study, it was given in 6.3 per cent of the cases, in precipitate labor, not at all. In prolonged labor it was used for the treatment of secondary uterine enertia. No anesthetic was given in natural or in precipitate labor. The forceps deliveries, with few exceptions, were carried out under parasacral or pudendal block anesthesia.

Case Finding

The children were chosen from those delivered between Jan. 1, 1934, and Dec. 31, 1945, inclusive. This population has been described in the preceding paper.

Every child delivered by high and midforceps was sought. Thirty were found. Seventeen more were located in the low forceps group.

After an operative case was selected and the child located, the nearest natural and precipitate labor cases were selected, in which the children corresponded in chronological age with the one in the operative group. This was determined by confinement number. We attempted to match parity in the operative and natural labor groups. There were discrepancies which are presented in Table I.

TABLE I. MATERNAL PARITY OF THE THREE GROUPS OF SUBJECTS

LABOR	NATURAL	PRECIPITATE	PROLONGED
DELIVERY	SPONTANEOUS	SPONTANEOUS	FORCEPS
Primiparas	29	2	41
Multiparas	14	43	6
Total No. Cases	43	45	47

The case finding was arduous and discouraging. Even with the help of the Chicago Board of Education and the Social Service Exchange, great difficulties were met. Every effort was made to locate the children in the operative group. Not so much effort was expended in the search for the children in the natural and precipitate groups. If a child could not be found within a reasonable time, the next one was sought.

After a child was located and the birth record abstracted, the medical social worker of the Center visited the home of the child and recorded the social history. The children were transported by car to and from Northwestern University Clinic, where they underwent pediatric, neurological, and psychological examinations and tests.

In the analysis of the data it was found that a small, but statistically significant, difference was present between the chronological ages of the three groups of subjects. For this reason, in analyzing the data, covariance was used to control for the differences in chronological ages.

The parents of the 65 Negro children were American born. The parents of 16 of the 70 white children were foreign born, and came from Mexico, Italy, Greece, France, and Poland. At the time the children were delivered, 66 per cent of the fathers had no employment or were on W.P.A. Thirty-six per cent listed their occupation as laborers, 10 per cent truck drivers, the remaining, farmers, steel workers, porters, clerks, house painters, musicians, salesmen, machinists, peddlers, and teachers. In 12 per cent, the father's name was legally withheld. Only one of these children was in the precipitate group.

Maternal Age and Birth Weight of the Subjects

The maternal age at birth and the birth weight of the subjects examined were plotted. In the natural labor division the mother's ages ranged from 16 to 33 years, with the largest number in the 16- to 19-year age group. In the precipitate group there were relatively few cases in the younger age categories. The peak occurred between 25 and 35 years. The age range was from 18 to 42. The peak in the prolonged labor with forceps division fell in the younger groups, and the range was from 16 to 35 years.

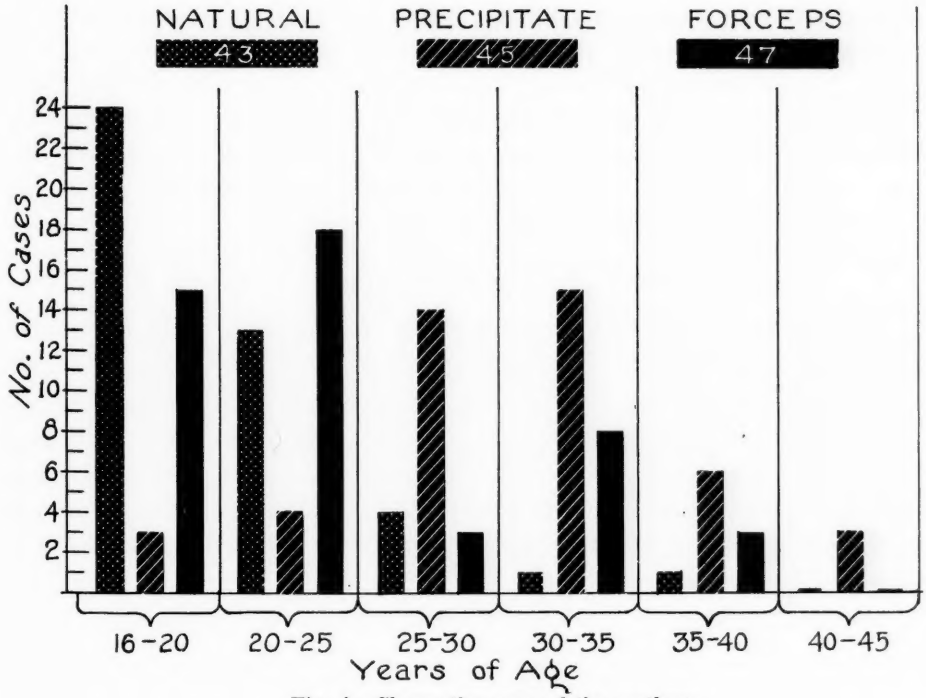

Fig. 1.—Shows the ages of the mothers.

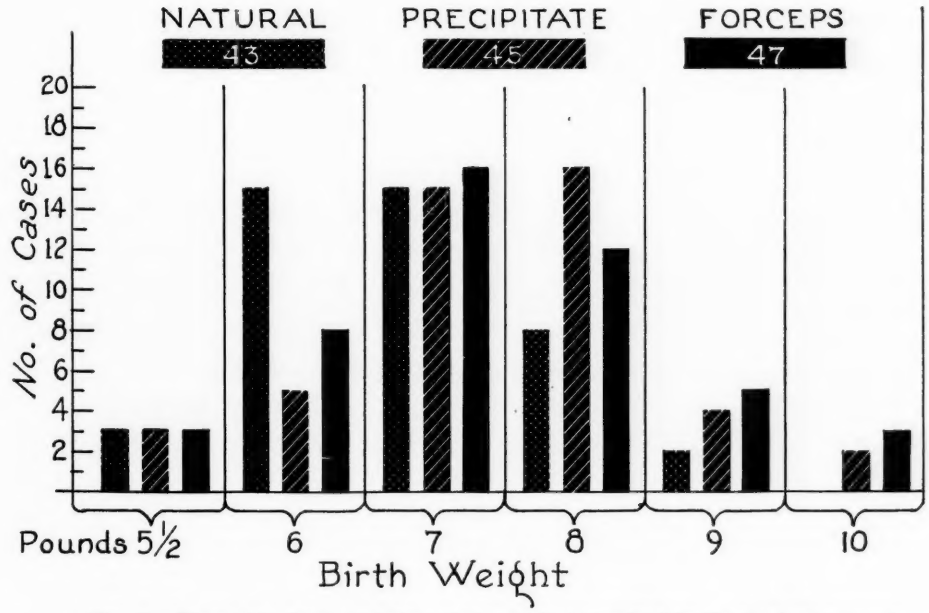

Fig. 2.—Shows the birth weights of the subjects studied in the various groups.

There was an equal number, 3, of 5½ pound babies in each division. The peak in the natural labor deliveries was found in the 6 and 7 pound groups. There was an abrupt fall in the 8 and 9 pound groups. The number of small babies was low in the precipitate labor unit. The peak was reached in the 8 pound group, and it fell gradually through 9 and 10 pounds. The incidence in the prolonged labor group reached a peak in the 7 pound babies, and fell gradually through 8, 9, and 10 pounds. Fig. 1 displays the maternal age and Fig. 2 the birth weights of the subjects.

Pediatric Clinical Findings

Specific data, exclusive of the birth experience, were obtained from the mother. School placement was recorded.

A complete physical examination was made on each child and the weight and height measured. A search was made for physical and developmental sequelae usually attributed to the child's birth experience. Agenesis, spasticity, idiocy, hydrocephalus, mental retardation, asymmetry of any portion of the body, claw hands, or any minimal changes were especially searched for.

X-rays of the wrists of 97 of the subjects were taken to determine bone age. Sight was tested by Snellen's and Massachusetts vision charts.

Physical Development.—

In general there was no difference in the physical development of the three groups of children, as determined by height and weight. However, there were 5 children who were way below par physically. Three were in the precipitate, and 1 each in the natural and instrumental groups. Of the 11 children judged physically superior, 4 were in the precipitate, 4 in the instrumental, and 3 in the natural group.

Bone Age.—

Todd's,[53] 1937, Table of Skeletal Maturation has established that the normal bone age approximately coincides with the chronological age, within a certain range of variation. The bone age of the subjects examined was correlated with the chronological age. A quotient was worked out by using $\frac{\text{X-ray bone age} \times 100}{\text{Chronological age}}$. Table II shows a close correlation of bone maturation and chronological age, irrespective of the type of delivery.

TABLE II. BONE AGE

LABOR		NATURAL		PRECIPITATE		PROLONGED	
DELIVERY		SPONTANEOUS		SPONTANEOUS		FORCEP	
RACE	SEX	QUOTIENT	NO.	QUOTIENT	NO.	QUOTIENT	NO.
White	Male	95.89	7	100.24	9	98.74	9
White	Female	103.50	8	96.62	8	104.81	8
Negro	Male	100.72	9	102.74	10	97.67	10
Negro	Female	106.41	5	99.11	10	98.76	4
Average		101.63		99.68		100.00	

Mental Retardation as Shown by School Placement.—

There were 10, or 8.33 per cent, of the 120 children who either failed two grades at school, or were in an ungraded room. An ungraded room is one in which the pupils are not engaged in equivalent studies, because of their inability to progress intellectually on account of physical and/or mental handicaps. Three of these children were in the natural labor group, 2 in the instrumental, and 5 in the precipitate groups.

There was no significant difference in the mental development of the children in the three groups, as judged by school progress ($P = 0.6682$).

Eyes.—

Seventy-seven per cent of the children tested had normal vision, and 23 per cent had defective vision. Eight hundred similarly tested children, at the University of Chicago Laboratory School,[54] 1951-1952, showed 18 per cent defective vision. Recent screening vision tests in the Chicago Public Schools revealed 11 to 13 per cent defective vision.[54] Fig. 3 gives the incidence of defective vision in the three groups.

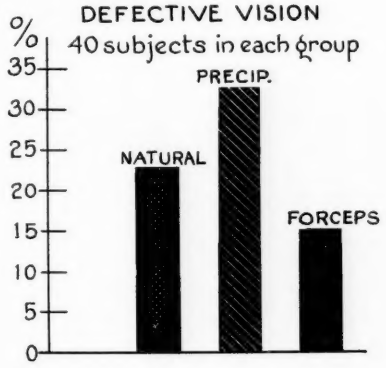

Fig. 3.—Shows the incidence of defective vision in the three groups.

One child in the precipitate group, with a tested vision of 20/100, has congenital nystagmus of the rotatory type, and is in a sight-saving class at school.

There was no correlation between eyes crossed at birth and those that developed later.

Defective vision was 10 per cent higher in children following precipitate labor with spontaneous delivery, than following natural labor and spontaneous delivery, and 17 per cent higher than following prolonged labor with forceps delivery. This difference could possibly be of significance ($P = 0.18$). This ratio would happen one out of five times, by chance, if there was no difference in defective vision in the three groups.

Apnea.—

Fourteen cases of apnea, classified as mild, moderate, and severe, occurred only in the prolonged labor forceps delivery group. None of these children showed physical or mental sequelae.

In conclusion we might state, from pediatric findings, that there is a slight indication that precipitate labor with spontaneous delivery is more detrimental to the development of the child than is either natural labor with spontaneous delivery, or prolonged labor with forceps delivery.

Neurological Findings

The incidence of neurological and psychiatric disorders among the series studied was determined by examination of the subjects, and by historical data obtained from their parents.

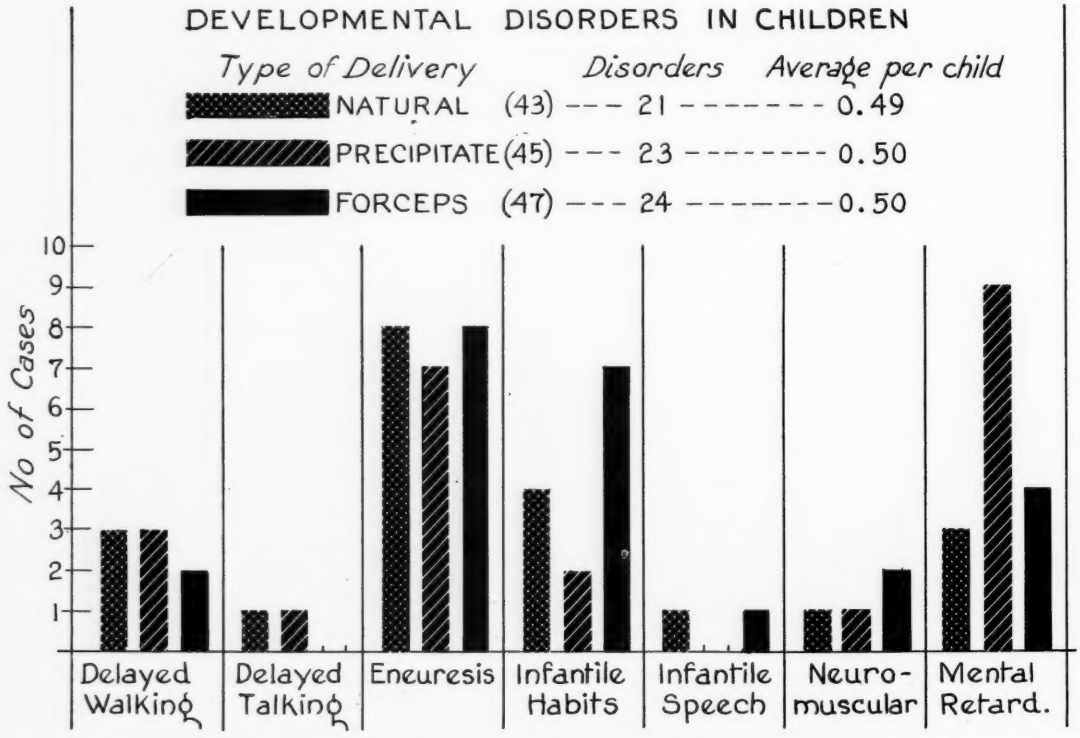

Fig. 4.—Shows the incidence of the various developmental abnormalities in the three groups of children.

The disorders found include a group in which there is delayed maturation of normal function or persistence of infantile abnormalities. This group includes delayed appearance of walking, delayed appearance of talking, enuresis past the age of 6, persistent infantile habits, such as thumb-sucking (past the age of 6), persistent infantile or lisping speech, persistent infantile neuromuscular awkwardness, and, finally, retardation in mental development. The incidence of these developmental abnormalities in the three groups of children studied is shown in Fig. 4.

As the figure shows, the total incidence of development disorders is not significantly greater in any group than in any other, but mental retardation is found more often in the precipitate group ($P = 0.0951$), while persistent infantile habits are appreciably greater in the prolonged group.

The remaining disorders of the nervous system found in the children studied include a history of epileptiform seizures, strabismus, behavior problems, emotional disturbances, focal neurological signs, stammering, and sleep-walking. Fig. 5 shows the evidence of these conditions in our subjects.

Again, it appears that no reliable differences are found in the incidence of these various neuropsychiatric disturbances. The greatest number occurred in the prolonged labor group. The probability of this ratio occurring by chance is one in twelve, or P = 0.08.

The incidence of focal neurological signs was greatest in the precipitate labor group.

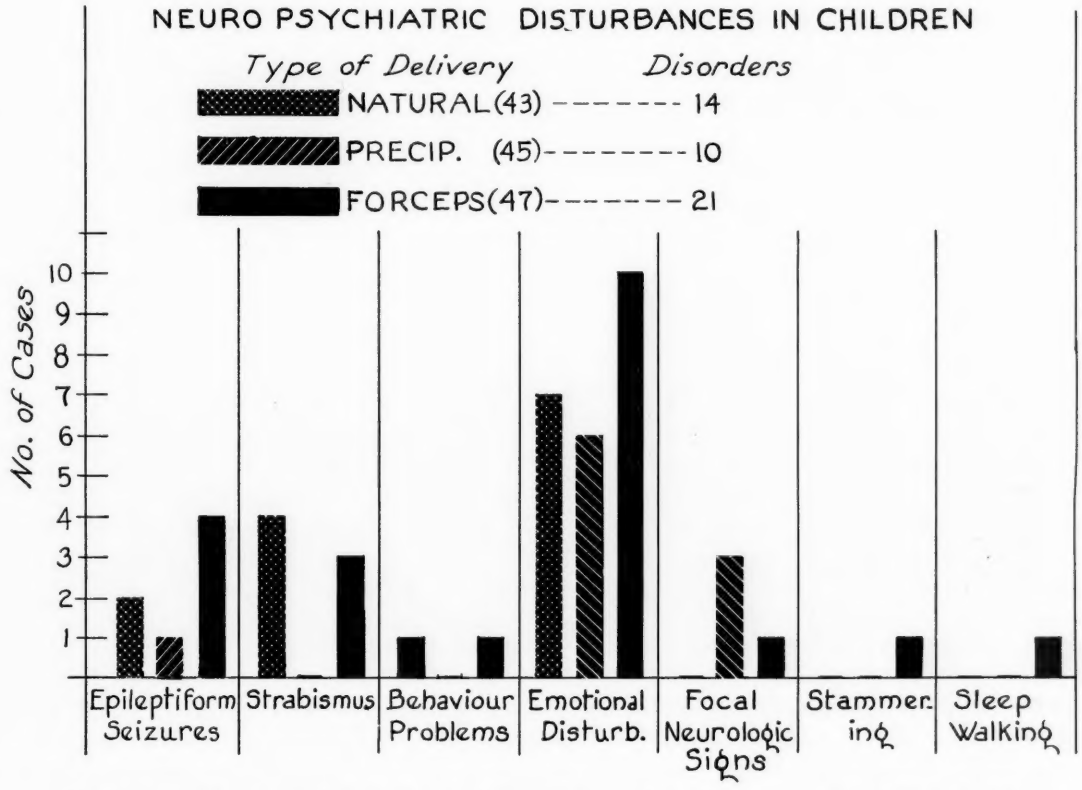

Fig. 5.—Shows the number of cases of various disorders of the nervous system in tne three groups.

Psychological Findings

The general procedures and the groups of subjects used in this study have been already described. The present report summarizes the results obtained in the psychological examination of the children. In this report the findings upon personality evaluation are not included and shall be reported later.

In the study reported here, the subjects were administered the Stanford-Binet Intelligence Test, Form L, and Porteus Mazes. Motor tests for laterality

in the use of the eyes, hands, and feet, and tests for speed of tapping and visual-motor performance in the completion of geometric figures were also administered.

The results are as follows:

1. There was no difference in the intelligence quotient of the Stanford-Binet, or in the performance of the Porteus Mazes among the three groups of subjects.

2. There was a significantly greater number of feeble-minded children in the precipitate group. The percentages of children obtaining I.Q.'s of 70 or less in the three groups are shown in Table III.

TABLE III

LABOR	NATURAL	PRECIPITATE	PROLONGED
DELIVERY	SPONTANEOUS	SPONTANEOUS	FORCEP
Number of Children	1	8	3
Percentage	2.5	20.0	7.5

The difference between the natural and prolonged delivery groups could occur by chance, but the probability that the precipitate group would show this difference due to chance factors is slight ($P = 0.01$ or 1:100).

3. There is also an indication that the precipitate group shows a greater dispersion over the mental ages in the Stanford-Binet Intelligence Test than do the children in the natural spontaneous or prolonged groups.

4. When the subjects of the precipitate and natural groups are matched for mental ages, a significant difference is found in their ability to reproduce figures such as a circle and a triangle. The performance of the children in the precipitate group is inferior to the performance of the controls.

5. There is some indication that the precipitate group does not have as clearly defined laterality in the use of the eyes, hands, and feet as do the natural or prolonged delivery groups. The children of the precipitate group show less consistency as to what side of the body they use in performing tasks involving the eyes, feet, and hands.

6. There was no difference among the three groups in the speed of tapping.

Summary

All of the results indicate that precipitate delivery is likely to be more deleterious than the spontaneous natural delivery or prolonged delivery with instrumentation. Children whose birth has occurred rapidly show a greater incidence of feeble-mindedness, a greater dispersion over the mental years in the intelligence test, a greater difficulty in completing geometrical figures, and a less well-developed laterality in the use of the hands, eyes, and feet.

All of these results taken in their totality are more characteristic of children who have suffered brain injury. It is, therefore, concluded that precipitate birth is more likely to result in brain damage than if the delivery is less rapid even though it may be prolonged and instruments have to be used.

Obstetrical Observations

It was found that if the child survived the neonatal period his chances of growth and development were the same after a prolonged labor with forceps delivery, as after natural labor and spontaneous delivery.

Following is an analysis of the labor records of the 47 children examined in the operative group. The average duration of labor was forty-two and a half hours, excluding the prodromal stage. The longest labor was ninety-one hours. The labors were characterized by primary or secondary uterine inertia, or both. This was treated by sedation. No Pituitrin was used. Five patients received Gwathmey analgesia. Ten per cent of the mothers were febrile, with a temperature above 101° F. There were 18 contracted pelves and 32 persistent posterior positions. Block anesthesia (parasacral block) was used for the delivery of 45 patients. General anesthesia (ether) was given twice. Table IV lists the operative procedures.

TABLE IV. TOTAL ANALYSIS OF 47 DELIVERIES

High forceps		4	47
Midforceps			
High mid	16	26	
Low mid	10		
Low forceps		17	
Dührssen's incisions			22
Manual or forceps rotation			32

All the babies had extensive molding of the head with large caput formation. Marked overriding of the sutures was observed, and 2 babies developed cephalhematomas. Two had transient facial paralysis.

The neonatal period was not remarkable in 32 cases. Four babies were hospitalized, 2 with a diagnosis of cerebral hemorrhage, 2 for atelectasis. Two children had marked tremors. In 1 convulsions were observed, while in 2 others the mothers gave a history of observing convulsions. There was 1 hematoma of the sternocleidomastoid muscle. One child developed bilateral abscess over the parietal bones.

Results of Apnea in Prolonged Labor and Forceps Delivery

Based on 12 cases (those with moderate and severe apnea) there was no difference in the growth and development of children who suffered from serious apnea following prolonged labor and forceps delivery and those who breathed spontaneously following prolonged labor.

This finding alone may have little significance because of the small number of cases, but considered together with the results of Hannes,[45] 1911, McPhail,[17] 1941, and Keith,[47] 1950, it gains in importance. They evaluated the development of 80, 34, and 111 apneic children, respectively. (Hannes' cases were operative deliveries, McPhail and Keith do not state the type of birth.) Their conclusions are the same as ours. The opinions of Darke,[22] and Preston,[23] who hold the opposite view, have been set forth previously.

An evaluation of the degree of anoxia experienced by the Center's children can only be surmised. Endotracheal oxygen was given to the babies immediately.

The ancillary sciences have thrown much light upon the subject of anoxia in the newborn.

The newborn infant tolerates oxygen lack to a much higher degree than the adult. Himwich,[34] 1941,[42] 1942, Miller,[41] 1949, and Wilson,[43] 1948, point out that special mechanisms are present which protect the fetus and newborn from oxygen lack. Himwich states that:

1. Fetal hemoglobin takes up more oxygen than adult hemoglobin, and releases it more readily.

2. The temperature drops markedly at birth and reduces the metabolic requirements.

3. An anaerobic metabolism, based on enzyme activity, supplements the oxygen metabolism in times of stress.

Furthermore, Himwich has shown in the dog,[41] 1941, and the rat,[55] 1941, that the cerebrum requires less oxygen than the lower brain at, and for two weeks following birth. He believes that this is in agreement with the low oxygen consumption of the cerebrum during this age of life. The reverse is true in the adult animal. The human newborn lives at the ganglion level and the cerebrum shows little function until the second week of life. Racker,[56] 1942, has repeated this experiment on two fetal brains and came to the same conclusion.

These experiments suggest that, if the baby survives, the oxygen needs of the cerebral cortex have been met, and no damage will occur due to oxygen lack alone. However, in the face of trauma, anoxia predisposes to cerebral hemorrhage.

Precipitate Labor With Spontaneous Delivery

Precipitate labor with spontaneous delivery was more deleterious to the growth and development of the child than either natural labor with spontaneous delivery or prolonged labor with forceps delivery.

Most of the births in the precipitate group were among multiparous women. Eighteen of the patients were in labor less than one hour. Probably cerebral injury did not occur in these cases due to the counterforces of labor. However, there are mechanisms acting in such cases which could lead to birth trauma. Contractions occurring too frequently, and with too much force, reduce the oxygen supply and lead to anoxia. This, in turn, can cause edema and hyperemia of the brain. Rupture of the bag of waters, with precipitate birth, produces sudden changes in intracranial pressure. Both of these conditions favor cerebral hemorrhage. There was an indication that focal neurological lesions were higher in the precipitate group, and mental retardation was significantly higher ($P = 0.01$).

Conclusions

1. If the child survives the neonatal period his chances of growth and development are equal after prolonged labor and forceps delivery and after natural labor with spontaneous delivery.

2. There is no difference in the growth and development of the child who suffers serious apnea after prolonged labor and forceps delivery and of the one that breathes spontaneously.

3. Precipitate labor and delivery are more deleterious to the growth and development of the child than either natural delivery or prolonged labor with forceps delivery.

Comment

The results of this work are not conclusive. The number of children studied is too small to warrant general application. The examining and testing were restricted to only one period. However, two purposes are served. First, it strengthens the validity of the opinion of certain observers, namely, Hannes, Sturma, and Keith, that difficult and apneic births do not contribute to a higher degree to abnormal mental development than spontaneous births, unaccompanied by apnea. Second, it has been a pathfinder for future research. It initiates and supports, within its scope, the hypothesis that precipitate labor is detrimental to the ultimate growth and development of the child.

A developmental clinic is needed to carry out this research. A correlation of birth experience with a continuous study of the growth and behavior pattern of the child may solve the problem of the effect of labor and delivery on the future development of the individual.

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Discussion of Papers* on Immediate and Remote Effects of Prolonged Labor With Various Types of Delivery on the Child

DR. WILLIAM J. DIECKMANN.—This report is important because of the long follow-up of the children and the careful studies made on them. As the authors state, previous reports of the sequelae of labor have been based on histories obtained from the children's mothers or from the adult patients (neither of whom can know the details of the deliveries) or from a study of usually inadequate labor records by some who are not obstetricians. To use records of some other hospital and base conclusions on the length of labor, the method of termination, and the period of asphyxia of the babies is absurd. I am certain that if each of us were given labor records, each would have a different interpretation.

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*The Immediate Effects of Prolonged Labor With Forceps Delivery, Precipitate Labor With Spontaneous Delivery, and Natural Labor With Spontaneous Delivery on the Child, by Beatrice E. Tucker, M.D., and Harry B. W. Benaron, M.D., page 540.

The Remote Effects of Prolonged Labor With Forceps Delivery, Precipitate Labor With Spontaneous Delivery, and Natural Labor With Spontaneous Delivery on the Child, by Harry B. W. Benaron, M.D., Meyer Brown, M.D., Beatrice E. Tucker, M.D., Vida Wentz, M.D., and George K. Yacorzynski, Ph.D., page 551.

The authors' reports indicate that a precipitate delivery causes more brain damage to the baby than a prolonged labor with forceps and decidedly more damage than spontaneous normal labor.

The authors state that 17 per cent of their deliveries were unattended and an additional 15 per cent of patients had no prenatal care. This is no reflection of them but is a reflection on medical care in the City of Chicago.

The ideal study would be to reproduce precipitate delivery by injection of solution of posterior pituitary, and prolonged labor by inducing labor before the cervix was "ripe," and then to compare the immediate and late results with those of spontaneous normal labor. However, we have learned by experience that the stillbirth and neonatal death rates and percentage of cerebral injuries were much higher when such obstetrics was practiced.

The authors have made as careful a study as is feasible in human beings. They have a much higher incidence of syphilis than we have but I doubt that it is the cause of the differences attributed to precipitate and prolonged labor.

I have no data comparable to this report but do have some results which were obtained in 1948 for a study similar to the authors' which was never completed. Table I contains data for mid- and a few high forceps for three years. It is worth noting that for the last two years studied there was a very definite decrease in the stillbirth and neonatal death rates and a decrease in the incidence of intracranial injury similar to that reported by other services.

TABLE I. MID- OR HIGH FORCEPS DELIVERIES

	1931-32		1938-39		1946-47	
	NO.	%	NO.	%	NO.	%
Patients	109		101		133	
Stillbirth	5	4.6	3	3.0	3	2.3
Neonatal deaths	3	2.8	5	5.0	0	
Birth injury	1*		1†		1‡	

*Depressed fracture (died).
†Subdural hematoma (died).
‡Fracture of clavicle, not additive.

These findings are further substantiated by a twenty-year study in the hospital during which time, for babies weighing 1,000 grams or more, there has been a marked decrease in the stillbirth and neonatal death rates and the deaths due to birth trauma, the majority of the latter by cerebral hemorrhage (Table II).

TABLE II. OPERATIVE DELIVERIES AND FETAL RESULTS, 1931-1951

		FORCEPS		VERSION AND EXTRACT.	CESAREAN SECTION	BABY DEATHS 1,000 GRAMS OR MORE		
YEARS	DELIVERIES	LOW %	MID- AND HIGH %	%	%	STILLBIRTH %	NEONATAL %	*BIRTH INJURY %
1931-1941	27,321	28.2	3.9	1.5	5.2	2.0	1.8	0.53
1941-1946	17,520	44.2	2.6	0.7	4.7	1.3	1.3	0.12
1946-1951	19,902	68.2	1.6	0.6	5.0	1.0	1.1	0.09

*Not additive to stillbirth and neonatal.
Clinical diagnosis of intracranial injury for 1946-1951 was made in 0.25 per cent of the babies as compared with 0.11 per cent for 1943-1946 and 0.05 per cent for 1951-1952.

The clinical diagnosis of intracranial injury by the pediatrician was much higher for the period 1946 to 1951 than for 1943 to 1946 and 1951-1952. There was no change in obstetricians during this period and the percentage of babies who died from intracranial injury decreased with each succeeding period (Table II).

We have no knowledge of the number of babies who showed no evidence of asphyxia or cerebral injury but were later found to be below the average.

It is worth noting that during this twenty-year period the cesarean section incidence has remained about the same but the incidence of operative deliveries, the majority being outlet or low forceps, has increased from 32 to 71 per cent. The reason for this increased forceps rate is that we believe: (1) Residents can be trained only by practice. (2) An outlet forceps with episiotomy by an experienced doctor causes less trauma than a spontaneous normal delivery. Our version and extraction rate should be higher for practice in selected cases. The authors' reports offer substantial proof that precipitate deliveries are dangerous to the babies and our data indicate that properly performed low forceps deliveries are not injurious.

From 1931 to 1942, at the Chicago Lying-in Hospital, the forceps rate was 32 per cent but patients would be in varying degrees of labor for as long as 100 hours. We learned by sterile vaginal examination that some of these patients were in false labor and they were sent off the delivery floor or home. Others were either delivered by cesarean section or by Dührssen's incisions and forceps after 18 to 36 hours of labor. Labor is not an endurance test between patient, fetus, and doctor. Frequent vaginal examination and periodic observations of the intensity, duration, and frequency of the uterine contractions must be made to determine: (1) Is the patient in labor? (2) Is labor progressing normally? (3) Is dystocia present? If the latter: (1) Is it due to a faulty uterine mechanism? (2) To tissues which will not dilate? (3) To a contracted pelvis? (4) A large baby? (5) Malposition? (6) Obstructing tumor?

We taught for many years that it was better for the baby undergoing a hard delivery if he were partially anesthetized, thus preventing aspiration of amniotic fluid, meconium, and blood from the vagina. For some years we have used some form of local or spinal anesthesia but I wonder if we should return to a procedure which may possibly be better for the baby.

Potter states that an anoxia exists when available oxygen falls below the physiologic needs of the organism. Unfortunately, no one knows how much or how little oxygen is required by the brain of the fetus in utero. The authors have stressed the fact that fetuses of different species or animals do not all give the same response to oxygen want and that animal experimentation cannot be transferred to human experimentation. Our studies of the oxygen content of blood obtained from the umbilical vein at cesarean section with the baby still in utero, under local anesthesia, range from 9.5 to 20 volumes per cent and the oxygen saturation ranges from 50 to 80 per cent. Barcroft and Huggett have studied the oxygen requirements in the sheep and goat for the animal as a whole and for the brain. I do not believe their studies can be compared with those made by us because they have delivered the fetus which remained attached to the placenta but the uterus was empty, and I do not believe the blood flow through the postpartum uterus is in any way comparable to what it is through the uterus with the fetus still in place.

Undoubtedly changes are present in the brain cells but the available histological staining methods are incapable of revealing them. In the last five years' study from our hospital, almost 20 per cent of the babies autopsied by Potter showed no pathologic cause for death. The physiology of the newborn baby must be studied. Microchemical methods are available.

These reports should be the preliminary work of an extensive program to determine what effect adequate maternal nutrition and care, the use or absence of sedatives during labor, types of anesthesia, types of delivery, nutrition of the baby and child have on the child's subsequent life. This should be a cooperative study of obstetricians, pediatricians, nutritionists, physiologists, psychiatrists, and schoolteachers.

THE OPINIONS OF PRIVATE PHYSICIANS OF A MEDICAL CARE PROGRAM

Experience in the Emergency Maternity and Infant Care Program in New York City

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EARLY in World War II, difficulties in providing obstetric and pediatric care to the families of servicemen led to establishment by Congress, in July, 1943, of the Emergency Maternity and Infant Care Program, popularly known as EMIC. The program was nationwide in scope, continued until July 1, 1949, and during this time spent $108,000,000 for 1,169,000 maternity patients and $14,000,000 for 217,000 infants. Eligibility for the program was limited to the four lowest pay grades in the services, upon application by wife of the serviceman. No new medical or hospital resources were developed for this program and those in existence were used according to established patterns of practice in the local community. Payment was provided for medical, hospital, nursing, and other types of care (ambulance, drugs, blood, plasma, and so forth), as needed. Each patient had free choice among the physicians willing to accept her under the program. Consultation was available upon request of the attending physician.

An important part of the program was the setting of certain minimum standards for hospitals and specialists included in the program. In general, these standards were set with the aid of local advisory committees in each state.

It is unfortunate that more studies of the EMIC experience have not appeared, for the problems related to distributing and providing health services in the country have long been of concern to both citizens and professional health personnel. For this reason all available data from the EMIC experience in New York City are being analyzed.[1, 2, 3]

During the six-year period of operation of the program, a total of 53,728 maternity patients and 12,837 infants were cared for in the city. The total cost was $7,377,356.58; the average cost for a maternity patient was $114.48 and for an infant, $95.53. The experience has been analyzed from the point of view of costs, administrative procedure and certain aspects of medical practice, related particularly to the kinds of physicians who cared for patients, consultants used, et cetera.

It seems clear that the program attracted many criticisms inevitable to any attempt to provide medical care on a large scale.[4] Some of these were certainly attributable to the wartime conditions under which the program operated and the fact that it grew so rapidly that there was little time for planning or consultation at federal, state, and local levels. Disinterested critical evaluation, however, needs to be approached from two angles: (1) accomplishments, the end result, and (2) mechanics, the means whereby the end was achieved. There have apparently been few complaints from those families who received service. Hospital administrators in general seem to have found the program a very satisfactory one, with fairly general agreement that the establishment of the formula for reimbursable per diem cost to purchase hospital care was a great step forward. The continued use of this device by private and public agencies seems to bear this out. Payment for hospital care was an important item financially, comprising, for example, 55 per cent of the EMIC funds expended in New York City[2] (in patient care for completed maternity cases only).

Relationships with physicians, however, raised other problems. No concrete or impersonal formula could be devised for establishing fees; wide variations existed in fees usually paid in different parts of the country and in urban and rural areas; specialists were accustomed to higher fees; certain procedures were sometimes restricted to specialists, a practice which rankled with general practitioners who had been accustomed to doing everything. In addition, payment on a cash basis involved for many the novel concept of an inclusive fee rather than fee-for-service and the ancient practice of allowing a cash allotment to the patient seemed more acceptable to some doctors. The following direct expression of opinions on their evaluation of the EMIC program by physicians in New York City who participated in it is therefore considered to be of particular interest.

Methods

Data were secured through three successive mailings of a questionnaire directed to all participating physicians and a final telephone interview of a random sample of the nonrespondents. In all, replies were received from 2,616 of the 5,575 physicians who cared for EMIC patients.

All 5,575 physicians participating were sent questionnaires during 1950; 1,356 replied. Another copy was sent to the nonrespondents; 726 more replies were received. To those who still had not responded, a short postcard with certain key questions was sent. There were 534 more replies to this. Finally, a random sample of the remaining nonrespondents was reached by telephone.

Despite all the difficulties inherent in the questionnaire method of obtaining information, it is believed that this study reflects reasonably accurately the opinion of all the physicians. In the first place, replies were received from about 50 per cent of those queried, which is considered an excellent response to a mailed questionnaire. Second, a comparison of the successive samples indicated that it seems doubtful that those who did not respond included a disproportionate number of either favorable or unfavorable opinions on the various items. Third, those reached by telephone gave reasons for not having responded previously which seemed, for the most part, unrelated to their opinion of the program, e.g., "Don't remember receiving questionnaire," "Had no opinions." Some, of course, could not be reached because of death or having moved out of the city.

Respondents included 64 per cent of the pediatricians, 55 per cent of the obstetricians, 48 per cent of the general practitioners, and 35 per cent of the other specialists; 64 per cent of those who had 10 or more cases, 51 per cent of those who had 3 to 9 cases, and 34 per cent of those with 1 or 2 cases.

To the general difficulties of any questionnaire method there is added in this case the difficulty of subjective opinion. These may of course vary with the doctor's general outlook on medical practice and with his particular relations with the Department of Health. The questionnaire included 14 specific questions and space was available for "yes," "no," and "no opinion" replies as well as over-all comments.

1. Do you think EMIC fulfilled its purpose of relieving enlisted men of anxiety regarding the availability and cost of obstetric and pediatric care for their wives and infants?
2. Do you think that the availability of the following services contributed to the better care of the patient?
   a. Consultations by specialists
   b. Special nurses
   c. Nurses of the Visiting Nurse Association
3. Do you think that applications of patients for care under the EMIC program were efficiently handled?
4. Do you think that authorizations for providing care under the EMIC program were efficiently handled?
5. Do you think that the payment of bills was efficiently handled under the EMIC program?
6. Were you satisfied, on the whole, with general administration of the EMIC program?
7. a. Do you think the fee paid to general practitioners for maternity care was a fair fee for this type of patient in New York City?
   b. If not, what should general practitioners be paid for this type of patient?
8. a. Do you think the fee paid general practitioners fair for well baby care, sick infant care?
   b. If not, what do you think the general practitioner should be paid for this type of patient?
9. Were you satisfied with method of payment under the EMIC program, whereby physicians and others were paid directly by the Department of Health at rates established under the program?
10. If not, would you have preferred cash payments by Department of Health to patients instead of direct payments to the physician and hospital?
11. Did you find the amount of "paper work" required in connection with applications, authorizations, and payment of bills more burdensome than bookkeeping for the average patient?
12. Was your professional relationship with EMIC patients different from your relationship with other patients?
    If yes—how different?
13. To be answered by specialists only.
    a. Do you think the fee paid to obstetric specialists for maternity care is a fair fee for this type of patient in New York City?
    b. Do you think the fee paid the pediatrician for well baby care and for sick infant care is a fair fee for this type of patient in New York City?
14. General comments.

Additional data on the respondents in relation to the questionnaires are found in Table I.

TABLE I. NUMBER OF PARTICIPATING DOCTORS AND NUMBER OF RESPONDENTS, BY FIELD OF PRACTICE OF DOCTOR, NUMBER OF CASES PER DOCTOR, AND QUESTION

	RESPONDENT TO:			
	QUESTIONS 1, 6, 7, 12a, 12b, 14 (ALL MAILINGS)	OTHER QUESTIONS (FIRST TWO MAILINGS)	NONRESPONDENT	TOTAL
Field of Practice.—				
Obstetrics	250	210	205	455
Pediatrics	194	167	139	333
General	1,866	1,465	2,041	3,907
Other specialties	306	240	574	880
	2,616	2,082	2,959	5,575
Number of Cases.—				
1-2	812	612	1,591	2,403
3-9	893	706	860	1,753
10 and over	911	764	508	1,419
	2,616	2,082	2,959	5,575

Results

The Success of the Program From the Point of View of the Care It Gave Patients.—

Questions 1 and 2 were designed to ask objective questions about the care patients received and the success of the program in meeting the "morale" problem.

1. Do you think EMIC fulfilled its purpose of relieving enlisted men of anxiety regarding the availability and cost of obstetric and pediatric care for their wives and infants?
2. Do you think that the availability of the following services contributed to the better care of the patient?
   a. Consultations by specialists
   b. Special nurses
   c. Nurses of the Visiting Nurse Association

Table II indicates the results. There has been fairly general agreement about the fact that the beneficiaries were satisfied with the program. It is not surprising therefore that of the 90 per cent of the doctors who gave a definite opinion on the question of EMIC fulfilling its purpose of relieving anxiety of enlisted men, 95 per cent said "yes." Unfortunately the 5 per cent answering "no" failed to qualify the answer with opinions regarding in what respect the program had failed.

TABLE II. OPINIONS OF PHYSICIANS CARING FOR EMIC PATIENTS CONCERNING THE PROGRAM FROM THE PATIENT'S POINT OF VIEW

	ALL CASES			CASES WITH DEFINITE OPINION	
QUESTION	% DEFINITE OPINION	% NO OPINION	% NO ANSWER	% YES	% NO
1. Did it relieve anxiety	90.1	4.8	5.1	95.0	5.0
2. Did availability of following help:					
a. Consultations	87.5	6.8	5.7	90.8	9.2
b. Special nurses	67.3	23.5	8.8	87.7	12.3
c. VNA nurses	71.2	19.9	8.9	93.2	6.8

Those who were in charge of administering the program would have thought that availability of consultation services and special services like nursing would be applauded without exception. Of the 87 per cent who answered the question on consultations, 90 per cent liked the idea of having specialists available. Only two-thirds of the physicians, however, answered the question regarding special nurses, perhaps because occasion to call upon them is not too frequent. The number of negative answers (12.3 per cent) may also be a reflection of the less frequent use of such nurses. Seventy-one per cent answered the question about visiting nurses. Of these, a high percentage, 93.2 per cent, thought they were valuable.

General Administration of the Program.—

The following specific questions were related to "paper work" and the administrative machinery.

3. Do you think that applications of patients for care under the EMIC program were efficiently handled?
4. Do you think that authorizations for providing care under the EMIC program were efficiently handled?
5. Do you think that payment of bills was efficiently handled under the EMIC program?
6. Were you satisfied with the general administration of the EMIC program?
11. Did you find that the amount of "paper work" required in connection with applications, authorizations, and payment of bills was more burdensome than bookkeeping for the average patient?

Table III indicates specific opinions on these questions. Between 84 per cent and 92 per cent had a definite opinion on these questions. About the same percentages (84 per cent to 92 per cent) were satisfied with the handling of applications, authorizations, payment of bills, and the general administration of the program. The highest number of negative opinions (20 per cent) was recorded for payment of bills. One cannot be sure that this actually reflects real differences in satisfaction with the administration of the program or is related to the amount of the fee paid. A small majority believed the paper work involved was not more burdensome than their ordinary bookkeeping. Most of the rest thought they were having to do extra work under the EMIC system. Those who devised the plan and worked it out were convinced that the system did not involve a single step more than the physician would have to take if he kept accurate books. Since many physicians are notoriously poor bookkeepers, it might be suggested that these answers refer to the physicians' own habits and since these habits are variable it is difficult to draw any conclusion.

These results do not seem to confirm the oft-quoted idea that the "red tape" involved with EMIC was overwhelming. The New York City experience may not be typical since the program was locally administered and there was a great deal of discussion of problems with individual doctors. Special effort was made by the Department of Health physicians who administered the program to simplify all procedures and to answer complaints promptly. Advisory committees with representatives of the local medical societies were widely used and were very helpful. Complaints about service of physicians were handled

by them and the existing committees of the county medical societies. When physicians in the EMIC administrative office called hundreds of doctors individually in an early evening telephone hour, it appeared that many difficulties were due to misunderstandings and that most of the complaining physicians had little idea of the complexities of handling the administrative problems. They seemed quite content to accept the existing routines when once they understood all sides of the questions raised. It is of course doubtful that any system of administration can be devised which will earn the approval of all of those participating.

TABLE III. OPINIONS OF PHYSICIANS CARING FOR EMIC PATIENTS CONCERNING ADMINISTRATIVE PROCEDURES

QUESTION	ALL CASES			CASES WITH DEFINITE OPINION	
	% DEFINITE OPINION	% NO OPINION	% NO ANSWER	% YES	% NO
3. Efficiency of handling applications	83.6	11.1	5.3	91.7	8.3
4. Efficiency of handling authorizations	87.0	7.2	5.8	89.6	10.4
5. Efficiency of payment of bills	90.1	4.1	5.8	79.9	20.1
11. Burdensome paper work	91.5	2.4	6.5	38.8	61.2
6. Satisfaction with general administration	88.2	5.6	6.2	84.4	15.6

Opinions Regarding the Adequacy of Fees.—

Any questions directed to find out what physicians thought about fees are in some way "loaded" questions. In an era of constantly rising prices and an inflationary spiral it is extremely doubtful that everyone will admit that any standard fee is fair. Physicians answering the questionnaire would certainly assume that the answers were going to be tabulated and used for some sort of analysis. It is hardly likely that they would jeopardize the chances of obtaining a higher fee either if the program were re-established or for payment through other sources by admitting that they were satisfied with a fee that had been paid before. In all likelihood such questions just cannot be answered satisfactorily by a questionnaire method. The questions used were as objectively stated as possible.

7. Do you think that the fee paid to general practitioners for maternity care was a fair fee for this type of patient in New York City?
   If not, what do you think a general practitioner should be paid for this type of patient?
8. Do you think the fee paid to general practitioners for well baby care and sick infant care was a fair one for this type of patient in New York City?
   If not, what do you think a general practitioner should be paid for this type of patient?
13. (To be answered by specialists only)
   a. Do you think the fee paid to obstetric specialists for maternity care is a fair fee for this type of patient in New York City?
   b. Do you think the fee paid to pediatric specialists for well baby care and sick infant care is a fair fee for this type of patient in New York City?

Results are summarized in Table IV.

TABLE IV. OPINIONS OF PHYSICIANS CARING FOR EMIC PATIENTS CONCERNING FEES

QUESTION	ALL CASES			CASES WITH DEFINITE OPINION	
	% DEFINITE OPINION	% NO OPINION	% NO ANSWER	% YES	% NO
7. Fairness of fee paid general practitioner for maternity care	81.0	12.4	6.6	22.4	77.6
8. Fairness of fee paid general practitioner for:					
Well baby care	56.9	32.8	10.3	48.0	52.0
Sick infant care	54.3	31.8	13.9	54.5	45.5
13. Fairness of fee paid					
a. obstetric specialist for maternity care	16.7	8.9	74.4	24.2	75.8
b. pediatric specialist for:					
Well baby care	12.0	12.3	75.7	45.2	54.8
Sick infant care	11.0	10.2	78.8	43.8	56.2

The difference of opinion regarding the fairness of fees paid for care of the mother and for care of the infant is striking. In some parts of the country the obstetric fee was considered good, but this did not hold in a large metropolitan area. Spontaneous criticism of EMIC in New York City was often directed at the small obstetric fee though physicians cooperated willingly because of the "wartime effort." On the other hand, almost half of the physicians thought the fee for pediatric work was fair, reflecting perhaps a closer approximation to existing standards or to the use of a system which paid so much per visit up to a maximum rather than a flat fee for all care given, as was true in the obstetrical cases. The range of the usual fee in pediatrics is much smaller than in obstetrics. There was a tendency for physicians to limit opinions on fees to their own category, i.e., particularly specialists and general practitioners.

There is, however, a substantial difference in opinion on fees when the opinions are analyzed separately according to the type of physician answering. The group most dissatisfied with the fees of the general practitioner were the general practitioners themselves. About half of the general practitioners thought the pediatric fee was fair—less than one-fifth thought the obstetric fee was fair. The obstetricians were more likely to think their own fees were bad than the fees of the others. It is interesting, however, to find that the reverse is not true, and that specialists other than obstetricians, including pediatricians, were more likely to think that the fees of pediatricians were fair than that the fees of obstetricians were fair.

Opinions Regarding Methods of Payment and Relationship to Patient.—In any system involving payments for medical care the question of method has always been the topic of much argument, particularly when the question of payment for physicians' services comes up. As soon as the source of payment shifts from the patient to some other group, private or public, complications arise. Thus EMIC fell heir to many old problems which have been thoroughly

explored elsewhere.[4] Three specific questions concerning this general topic were directed to the physicians in this study.

9. Were you satisfied with the method of payment under the EMIC program, whereby physicians and others were paid directly by the Department of Health at rates established under the program?
10. If the answer to question 9 is "no," would you have preferred a program in which uniform cash payments were made by the Department of Health to patients instead of direct payments to the physician and hospital?
12. Was your professional relationship with EMIC patients different from your relationship with other patients?
If yes, how different?

The results are tabulated in Table V. Questions 9 and 10 are of course related. Ninety per cent of the physicians had a definite opinion on the method of payment and 90 per cent of these thought the system of payment directly to the physicians was fair. Furthermore, more careful analysis of the answers indicates that only 8 per cent of the respondents preferred cash payments to the patients. It would appear from replies to these questions that only a very small minority of physicians in New York City were dissatisfied with a system which arranges for payment directly to the physician for services rendered and very few would like to see payments made to the patients. The possibility of capitation or any sort of salary was not brought up in this questionnaire.

TABLE V. OPINIONS OF PHYSICIANS CARING FOR EMIC PATIENTS CONCERNING METHODS OF PAYMENT AND RELATIONSHIP TO PATIENTS

QUESTION	ALL CASES			CASES WITH DEFINITE OPINION	
	% DEFINITE OPINION	% NO OPINION	% NO ANSWER	% YES	% NO
9. Satisfied with direct payment	89.8	3.1	7.1	90.1	9.9
10. If not satisfied with direct payment, preferred cash grant to patient	25.8	2.5	71.7	25.9	74.1
12. Change in professional relationship to patient	93.8	0	6.2	8.1	91.1

It is of considerable importance that the physicians who cared for EMIC cases felt that there was no difference in the professional doctor-patient relationship for EMIC cases than for other patients. Even of those who thought the relationship to be different, almost one-fifth thought it was *better* because of EMIC than in the ordinary situation.

Comments on the Program.—

One question (No. 14) read, "What comments do you have on the EMIC program?" The answers to this question were broken down according to approval and disapproval. Only one-third of the respondents answered this question at all. Of these, almost one-third gave unqualified approval to the program; a little better than one-fifth gave qualified approval. Thus, more than half of all the physicians who commented were generally in favor of the pro-

gram. A few were ambiguous in answers but 42 per cent gave some sort of disapproval and 5 per cent unqualified disapproval. Again, it is hardly likely that any scheme of medical care will be found at any time which will not have some 5 per cent who will not like it in any way, shape, or form.

Differences in Opinion Between Specialists and Nonspecialists.—

Reference has been made above to the different opinions on fees from specialists and nonspecialists. Answers to all questions were analyzed to see what differences, if any, were found among four groups, i.e., obstetricians, pediatricians, other specialists, and general practitioners. It is surprising how little difference there was among the opinions of physicians in different fields of practice in regard to details concerning consultation services and methods of administration (Questions 2, 3, 4, 5, 6, 11). There is little difference, too, with regard to their reaction to the method of payment. The obstetricians, however, were distinctly ahead of their colleagues in requesting a cash payment to the patient; about one-third thought this would be a good idea. The general practitioner was much less likely to object to the paper work than was the specialist. Pediatricians seemed to complain more about paper work than the obstetricians, perhaps because the clinical report regarding infants was in more general terms. There seemed to be no great difference between general practitioners and specialists in regard to physician-patient relationship.

There is little to choose from in the reactions of the four groups to the success of the program in fulfilling the objective of relieving anxiety, but it is surprising that only one-fourth of the general practitioners had a definite opinion. Thirty-five per cent had no opinion and 39 per cent did not even answer. Apparently, general practitioners were more willing to answer specific questions concerning details than they were to commit themselves regarding the total program and its value.

As might have been expected from the other comments up to now, obstetricians were less likely to give approval to the entire program (Question 14) than pediatricians or general practitioners. Apparently, by and large, pediatricians were more satisfied. Almost two-thirds of the pediatricians expressing an opinion gave some sort of approval to the program. These generalizations are based only on the specific comments written in to answer the broad question asking for comments (Question 14). They are not consistent with the reactions to specific questions.

Effect of More Active Participation in the Program.—

The data on all the questions were tabulated according to the number of cases the physician had—broadly into three groups: those who had only 1 to 2 cases, those who had 3 to 9, and those who had 10 and over. Roughly one-third of the physicians fell into each of these categories. After a review of the individual questions, it is noted that in general more cases are associated with more favorable opinions of EMIC. Two possible interpretations, however, may be made of this fact: first, the greater approval is based upon the fact that a physician who rather liked EMIC from the beginning tended to accept more

patients and more patients tended to come to him; second, it is possible that a physician who had a large number of patients came to know the program better and that liking increased with knowledge. In other words, while greater liking for the program was associated with more cases, it is difficult to tell which was cause and which effect.

Comment

Some conclusions may be drawn, although cautiously, from the data which have been presented, with the possibility kept in mind that even though the sample was 50 per cent and thought to be representative, those who did not answer may have had different opinions. In view of much of the original objection and grumbling at the time EMIC was started, it is gratifying to note that more than half of the physicians approved of the program in general. It is equally gratifying and surprising that an even higher number thought that the program achieved its objective. Apparently those who thought it achieved its objective but did not approve of it felt that some sort of modification would be necessary in order both to achieve the objective of the program and to satisfy the physician. It is also interesting to note that there was not very much objection to the paper work involved. Those who were concerned during the early hectic days of the program with trying to devise simple methods that would give required administrative information and yet not burden the physician cannot help but be pleased that their objective was apparently reached. It would seem also that there is little basis for fear that a program like EMIC will interfere substantially with patient-physician relationships. It appears that the majority of physicians are satisfied with a method of payment which does not involve the patient handling the money. While there is less than unanimity on this question there is too little disagreement to justify going over to a cash payment system which was itself approved by only a very small percentage of the physicians.

Failure to appreciate help of specialists was surprising. It was not clear what the reason for this is—possibly lack of availability, standards which interfered with physicians using their regular consultants, or just lack of recognition that consultants are necessary in a significant number of cases.

The big disagreements were in fees. The obstetrical fee, in particular, was considered too low in an urban area. Just where it should be set, or how, is not clear from this study.

This study suggests that similar studies of what participating private practitioners of medicine feel about various public and voluntary insurance and other medical care plans in which they are involved would be of value. Different patterns for providing medical care are being tried out in this country and it certainly seems that they should be evaluated in every way possible. Not the least of these evaluations is found in the opinions of the doctors who themselves care for the patients concerned. The opinions of the recipients of care under such programs should also be investigated.

Summary

The opinions of all physicians (a total of 5,575) who themselves cared for EMIC patients in New York City during World War II were solicited through a questionnaire with specific questions to which "yes" or "no" or "no opinion" answers could be given. About 50 per cent of physicians responded and this group of respondents was found to be representative of the entire group who cared for patients. Data were secured through three separate mailings and one telephone inquiry to a random sample. The similarity of the data so collected and the unusually large number of returns make it sound to conclude that this study reflects reasonably accurately the opinions of all the physicians in the community who cared for EMIC patients.

About 90 per cent thought the program reached its objective of raising morale. Slightly fewer, but still more than three-fourths of the total, were satisfied with the procedures of application and authorization and with the general administration of the program. More than 90 per cent were satisfied with the method of payment directly to the physician and only a very small number, fewer than 1 per cent, would have preferred a cash payment to the patient.

More than 90 per cent of the physicians thought that the functioning of the plan had not interfered with the patient-physician relationship. Of the small number who thought the plan had produced a change, almost one-fifth thought it made the relationship better rather than worse. Pediatricians seemed more likely to think it better.

Availability of consultation services was generally appreciated but there was not as much positive expression of approval for special nursing service as for medical consultation by specialists and services of visiting nurses.

The greatest dissatisfaction was in the amount of the fee paid, particularly the obstetric fee. In general, more participation, i.e., caring for a greater number of cases, was associated with a more favorable opinion of EMIC.

This analysis is thought to be unique in that it is apparently the only one recorded so far in which the opinions of physicians who actually cared for EMIC patients in a community have been secured and analyzed. It is suggested that similar studies of the opinions of the physicians participating in and the patients receiving care from the many medical care programs now being tried out in this country be made.

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CONGENITAL ANOMALIES OF THE UTERUS ASSOCIATED WITH PREGNANCY: AN ANALYSIS OF ONE HUNDRED EIGHTEEN CASES FROM THE LITERATURE WITH A REPORT OF NINE ADDITIONAL CASES*

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THE obstetrical literature is replete with many case reports concerning the association of pregnancy and malformations of the female genital tract.[1-71] However, until the very thorough review of the subject by Jarcho[1] in 1946 and the recent contribution of Fenton and Singh,[2] no authoritative study of this condition has been undertaken in the past decade. Our interest in the subject was initially motivated by the relatively high incidence of uterine anomalies discovered in our prenatal clinic since Jan. 1, 1950; and secondarily by the paradoxically low incidence of cesarean section and other operative procedures utilized in the management of our cases during that same period. With our own experience uppermost in mind, we decided to study the problem from the standpoint of proper management as measured by the yardstick of a minimum of fetal mortality in each group. To accomplish this task we reviewed all the reported cases of pregnancy associated with congenital uterine anomalies published in the English and French literature during the period 1930 through 1951.[3-71] These reports were all subjected to a very careful analysis and the results of the study were compared with the present accepted normal incidence of certain complications of pregnancy as well as with the incidence of complications occurring in congenital malformations of the uterus as reported by the Sloane Hospital Group.[2] The statistical analysis of 118 reported cases[3-71] and of our 9 additional cases and the conclusions and recommendations resulting from this study comprise the basis for this presentation.

Etiology

The cause of malformations of the female genital tract is not completely known. In early embryonic life the Müllerian ducts give rise to the uterus, both tubes, and the upper two-thirds of the vagina if nothing occurs to disturb

*This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

normal development. However, if this normal sequence is disturbed and fusion of the Müllerian ducts fails to occur completely or in part, the result will be an anomalous development of the uterus and vagina or both. For more detailed information regarding the embryology of the female genital tract, it is suggested that any standard text be consulted or Jarcho's[1] paper be reviewed.

Classification

Several classifications of this group of anomalies have been suggested in the past but only to result in more confusion and unwieldy nomenclature. We felt the classification advocated by Jarcho[1] was logical and quite informative and will use it entirely throughout this study. For convenience, however, we will refer to each type of anomaly, respectively, by letter as noted in Fig. 1.

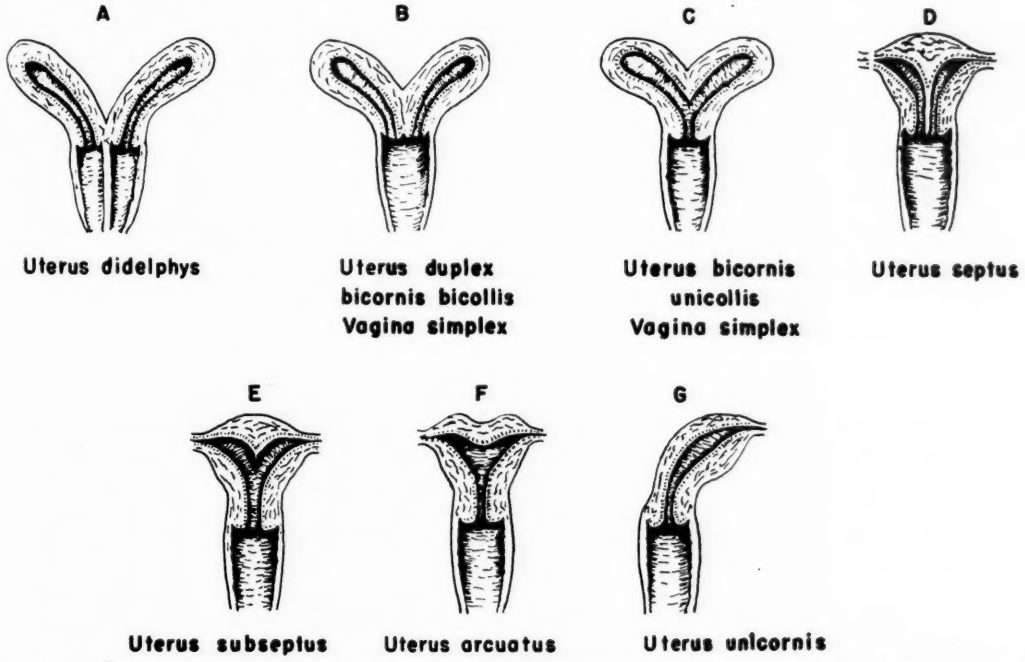

Fig. 1.—Schematic drawings of congenital uterine anomalies. (After Jarcho, J.: Am. J. Surg. 71: 106, 1946.)

Incidence

The reported incidence of this condition has varied considerably and for good reason.[1, 2] There is no definite figure that can be quoted as it depends upon the degree of individual interest displayed by everyone practicing obstetrics and the number of cases finally appearing in the available literature. It has been our personal impression that the condition is much more frequently encountered if it is only kept foremost in mind. An incidence of 0.3 per cent of all deliveries from Jan. 1, 1950, through Dec. 31, 1952, in our hospital was noted to be associated with congenital anomalies of the uterus.

Diagnosis

The problem of antepartum diagnosis will also depend upon the individual interest displayed by each examiner. Groups A, B, and C should offer no problem in diagnosis if a thorough bimanual examination is performed at the first prenatal visit plus a speculum examination to reveal a double cervix and vagina. The other groups will more often not be discovered until special examination procedures are carried out in each case. It is recommended that all sterility cases, habitual aborters, patients with premature labors, and those who have unexplained stillbirths be studied by hysterosalpingography as soon as feasible in order to bring to light any anomalous development of the uterus not manifest on ordinary pelvic examination. In this manner more cases in Groups D, E, F, and G will be discovered and the proper course in management will then be afforded the patient. In this study 59.1 per cent, or 75 cases, were diagnosed antenatally, 2.4 per cent were discovered at the time of surgery, and 49, or 38.6 per cent, were not diagnosed until after delivery. This record, we feel, could be improved upon if the measures recommended above were routinely put into practice.

Fertility

Most investigators considered the fertility of individuals with anomalies of the uterus to be subnormal. However, in recent years it has become evident that such a concept is not correct, as brought out by previous reports[1, 2] and as confirmed by this study. Our total of 127 cases accounted for 275 pregnancies, an average of 2.16 pregnancies per patient.

Material and Method

One hundred twenty-nine cases of pregnancy associated with some form of congenital anomaly of the uterus were originally abstracted from the literature and along with our own 9 cases analyzed according to a definite plan. Eleven case reports were considered to be deficient in certain pertinent data and were deleted from the study. This left a total of 127 cases for analysis and reference to Table I will reveal all pertinent data obtained from the study grouped according to the type of uterine anomaly present. From this basic information it was possible to analyze statistically the incidence of abortion, fetal mortality, malpresentation, operative delivery, maternal mortality and morbidity, complications of pregnancy and labor, fetal anomalies, and other miscellaneous data and compare them with certain accepted normals as well as with the incidence of similar abnormal data from another study.[2] During the actual analysis of our study, it was noted that the largest number of cases were found under groups A and C, amounting to 38.6 per cent and 46.5 per cent, respectively, and the remainder accounted for 19 cases, or 15.0 per cent. It was therefore decided to compare the total cases in Groups A and C with all others and with the normal as it was conceded that the cases contained in the other groups were too small in number to have any statistical significance. With this working plan in mind, the following information was obtained.

Data Obtained From Analysis of 127 Cases of Uterine Anomaly

Incidence of Uterine Abnormality in Relation to Type.—

Of the 127 cases of uterine anomaly and pregnancy reported here, 46.5 per cent were in Group C, 38.6 per cent were in Group A, and 15.0 per cent

TABLE I. COMPILATION OF DATA FROM LITERATURE SURVEY OF DOUBLE UTERI ASSOCIATED WITH PREGNANCY

CLASSIFICATION OF VITAL STATISTICS	TYPE OF UTERINE ANOMALY							TOTAL
	A	B	C	D	E	F	G	
Total cases studied	49	2	59	6	6	1	4	127
Number of viable births	45	2	38	5	3	1	4	98
Number of abortions	4	0	16	1	3	0	0	24
Number of infants	48	2	46	5	3	1	4	109
Number of fetal deaths	2	0	11	0	0	0	1	14
Operative deliveries	31	1	30	1	2	1	2	68
Cesarean sections	25	1	13	1	0	0	1	41
Nonoperative deliveries	16	1	16	4	1	0	2	40
Complications of pregnancy	32	2	21	0	3	0	2	60
Complications of labor	37	2	24	3	1	0	2	69
Maternal morbidity	8	1	14	0	3	0	0	26
Maternal mortality	0	0	3	0	0	0	0	3
Fetal anomalies	3	0	0	0	0	0	0	3
Miscellaneous operative procedures	6	0	11	1	0	0	3	21

included all the others. Anomalies of Group C are significantly higher than all the others combined and about three times as frequent in occurrence as all others. Anomalies of Group A are significantly higher than all others and occur about three times as frequently. Groups A and C do not differ statistically.

Percentage of Viable and Term Births.—

Considering 1,500 grams as the measure of viability, in our study there were 98 viable infants, or 77.2 per cent. If we subtract 25 viable premature infants, we have 73 viable term infants, or 57.5 per cent of 127 cases. Comparison of these figures with the normal as reported by the Sloane Hospital Group, 93.1 per cent and 85.0 per cent, respectively, reveals a significant decrease in both term and viable births in this anomalous group.

Incidence of Abortion Related to Type of Abnormality.—

Our study included 24 abortions or pregnancies surgically removed prior to the stage of viability from a total of 127 pregnancies, an incidence of 18.9 per cent. Table II contains the abortion incidence (surgical and spontaneous) for Group A, Group C, all others combined, and the normal. It will be noted that Type C has about three times the abortion rate of Type A and five times the abortion rate of the normal and this is highly significant statistically. On the other hand, Group A does not differ significantly from the normal. This may be explained by the relatively decreased vascularity of the dividing septum and distorted interior of the Group C uterus, resulting in a poor implantation bed and hence more frequent abortion.

TABLE II. INCIDENCE OF ABORTION RELATED TO TYPE ABNORMALITY AND IN THE NORMAL UTERUS

CLASSIFICATION OF UTERUS	INCIDENCE OF ABORTION
Group A	8.2%
Group C	27.1%
All other groups	21.1%
Normal uteri	5.6%

In the compilation of the 24 pregnancies terminated prior to viability, it was noted that one was an ectopic pregnancy removed at laparotomy, 9, or 7.1 per cent, were spontaneous abortions, and 14 were pregnancies removed by dilatation and curettage, hysterectomy, or other surgical procedure prior to the stage of viability of the fetus. One of the curettage procedures was a therapeutic abortion for toxemia of pregnancy.

Stillbirth and Neonatal Mortality.—

From a total of 127 pregnancies, there resulted 109 infants. This figure included 6 sets of twins, which is greater than the normal incidence. Of the 109 infants delivered, there resulted 14 fetal deaths, an uncorrected incidence of 12.8 per cent. Two infants weighed under 1,500 grams, two were macerated, and one was undelivered at seven months' gestation due to the death of the mother. When these deaths are subtracted, we have a total of 9 for an incidence of 8.7 per cent corrected fetal mortality.

Fetal Mortality Related to Type of Uterine Anomaly.—

Further analysis of our cases revealed that 2 infants, or 4.3 per cent, died in Group A, 11, or 23.9 per cent, in Group C, and one, or 6.3 per cent, in all others. The five unavoidable deaths occurred in Group C. Group C had a fetal mortality of six times that of Group A (23.9 per cent versus 4.3 per cent) and this difference is statistically significant.

Fetal Mortality Related to Type of Presentation.—

When the total fetal mortality was analyzed from the standpoint of presentation, it was noted that 6 deaths occurred in 51 vertex presentations. Two of these were unavoidable and gave rise to an incidence of 7.8 per cent. Surprisingly, only one death occurred in 30 breech presentations and this was unavoidable; therefore, no mortality could be charged to breech presentation in our series. There was one death in 3 transverse presentations which was avoidable and this resulted in a corrected fetal mortality of 33.3 per cent. Twenty-five presentations were not listed in our study and from this group came 6 of the infant deaths, a gross incidence of 24.0 per cent. However, 2 of these cases were unavoidable and the corrected fetal mortality in this group was noted to be 16 per cent. From this analysis it would appear that breech presentation gives rise to a lower fetal mortality which would certainly not be expected.

Method of Delivery Related to Type Anomaly and Presentation.—

If a further analysis of the fetal mortality is made in relation to the type of anomaly and method of delivery, the following information is obtained as shown in Table III. There were thirty spontaneous deliveries, or 27.8 per cent of all deliveries, and these resulted in 2 infant deaths. Two versions and extractions, or 1.9 per cent of all deliveries, accounted for 2 more infant deaths. One fetal death occurred in a laparotomy on a woman seven months pregnant, presumably done for a rupture of the pregnant horn. Another occurred as a result of the mother's death following exploratory laparotomy. There were 41 cesarean sections that resulted in 6 infant deaths. After correcting for two infants, there remained a corrected fetal mortality of 9.8 per cent. Twenty-two cases were classical sections and resulted in a corrected fetal mortality of 4.5 per cent. Fourteen cases were low cervical sections and resulted in 7.1 per cent corrected fetal mortality. One of these low cervical sections was done by an extraperitoneal approach according to the Waters technique. There were five Porro type cesarean hysterectomies that accounted for 2 infant deaths, and it is generally conceded that the complications produced the deaths and not the operative procedure. The over-all incidence of operative delivery was 63.0 per cent and resulted in a corrected fetal mortality incidence of 10.3 per cent. There were 40 nonoperative deliveries, or 37.0 per cent, that resulted in a corrected fetal mortality incidence of 5.0 per cent. From this it would appear that spontaneous delivery results in a lower fetal mortality and, therefore, is the procedure of choice under such circumstances. However, the difference for this series of cases is not statistically significant.

TABLE III. METHOD OF DELIVERY RELATED TO TYPE OF ANOMALY AND FETAL MORTALITY

METHOD OF DELIVERY	OVER-ALL NUMBER	INCIDENCE (PER CENT)	TYPE ANOMALY A	TYPE ANOMALY C	TYPE ANOMALY OTHERS	INFANT MORTALITY NUMBER	INFANT MORTALITY PER CENT
Nonoperative	40	37.0	16	16	8	3*	5.0
Spontaneous	30	27.8	11	11	8	2	6.7
Assisted breech	9	8.3	5	4	0	0	----
Undelivered	1	0.9	0	1	0	1*	----
Operative	68	63.0	31	30	7	11*	10.3
Cesarean section	41	38.0	25	13	3	6*	9.8
Classical	22	20.4	13	8	1	3*	4.5
Low cervical	14	13.0	11	1	2	1	7.2
Porro hysterectomy	5	4.6	1	4	0	2	40.0
Low forceps	13	12.0	2	8	3	1*	----
Breech extraction	8	7.4	3	4	1	1*	----
Midforceps	3	2.8	1	2	0	0	----
Version and extraction	2	1.9	0	2	0	2	100.0
Laparotomy	1	0.9	0	1	0	1	100.0
Total	108	100.0	47	46	15	14*	8.7
Infant deaths			2	11*	1		
Corrected fetal mortality per cent			4.3%	13.0%	6.3%	9	8.7

*Five unavoidable deaths; two from classical section group.

A comparison of cases in Groups A and C revealed no significant difference between the incidence of operative and nonoperative deliveries. It was noted, however, that there were twice as many operative deliveries in Groups A and C as there were spontaneous deliveries, in all others, they are evenly distributed. Also, in Group A cesarean section was required in 53.2 per cent of 47 cases, as compared with 28.3 per cent of 46 cases in Group C, a very significant difference. This increased incidence of cesarean section in Group A may be explained by the rather widespread reluctance of obstetricians to allow a patient to continue in labor and deliver vaginally with the constant threat present of obstruction from the nonpregnant horn.

Fetal Weight and Fetal Mortality Related to Anomaly.—

Upon further analysis of the fetal deaths in relation to the weight of the infant and the type of uterine anomaly, the following facts were determined: There were 48 infants in Group A, 46 infants in Group C, and 15 infants in all other groups. Group A had 14 infants under 2,500 grams and Group C had 8 infants under 2,500 grams, a fairly significant difference. However, the highest fetal mortality, after making corrections for 5 infants, occurred in the group over 2,500 grams and probably lessens significantly the effect of fetal weight on fetal mortality in this study.

Maternal Mortality and Morbidity and Type of Anomaly.—

There were 3 maternal deaths in our study, an incidence of 2.4 per cent. One occurred on the eleventh postoperative day following an emergency laparotomy for rupture of the pregnant horn at twenty-four weeks' gestation; one followed another laparotomy at seven months for presumably a ruptured pregnant horn and death occurred in the fifth postoperative day from excessive bleeding; the third death resulted from a laparotomy at about thirty-two weeks' gestation. There was a concurrent tuboovarian abscess present that was ruptured during the surgical procedure and the patient died undelivered of acute peritonitis on the fourth postoperative day. There was a total of 26 cases with morbidity, an incidence of 20.5 per cent. Reference to Table IV will reveal the various postpartum complications that contributed to the incidence of morbidity. Group C had 14 cases, Group A had 8 cases, and all

other groups accounted for 4 cases. The greatest incidence, it will be noted, occurred in Group C. This morbidity incidence in Group C is almost twice that in Group A and is probably not due to chance.

TABLE IV. POSTPARTUM COMPLICATIONS PRODUCING MATERNAL MORBIDITY

COMPLICATIONS	A	C	ALL OTHERS	TOTAL
Pulmonary embolus	0	1	0	1
Retroversion	0	1	0	1
Postpartum hemorrhage	1	4	1	6
Abscess with fever	1	1	0	2
Atelectasis	1	0	0	1
Pneumonia	2	0	0	2
Peritonitis	1	1	0	2
Subinvolution	0	2	1	3
Endometritis	0	2	0	2
Anemia	0	1	1	2
Pericarditis with effusion	1	0	0	1
Passage decidual cast	0	1	0	1
Unexplained fever	1	0	0	1
Infected episiotomy	0	0	1	1
Total	8	14	4	26

Complications of Labor Related to Type of Anomaly.—

The complications of labor in this study occurred in a total of 69 cases. There were 37 in Group A, 24 in Group C, and 8 in all other groups. The largest number of cases resulted from premature labor and were evenly divided between Groups A and C with 7 each. Obstruction from the nonpregnant horn occurred 8 times in Group A, 3 times in Group C, and only once in all others. Retained placenta was found in 9 instances: 5 in Group C, 3 in Group A, and only once in all other groups. Ruptured membranes over twelve hours occurred 6 times in Group A, twice in Group C, and only once in all other groups. The rest of the complications were fairly evenly distributed and in order of importance were uterine inertia, severe laceration, miscellaneous, prolonged labor over twenty-four hours, and hemorrhage. The increased incidence of labor complications in both the uterus didelphys and the uterus bicornis unicollis was considered quite significant and must be anticipated when managing this type of case.

Complications of Pregnancy in Relation to Anomaly.—

There was a total of 60 complications of pregnancy in the study. Thirty-two occurred in Group A, 21 in Group C, and 7 in all other groups. Malpresentation occurred most frequently in Group A with 18 breech and one transverse lie. Group C contained 12 malpresentations with 10 breech and 2 transverse. All other groups accounted for 2 breech, one face and one brow that was successfully converted to a posterior occiput. Premature rupture of the membranes was next most frequently noted and occurred 9 times in all. Six cases were encountered in Group A, 2 in Group C, and only one in all other groups. The remaining complications were mostly found in Groups A and C but were too few in number to be of any statistical significance. In order of frequency, they were surgical conditions, toxemia of pregnancy, third trimester bleeding, medical conditions, and certain miscellaneous complications.

The extremely high incidence of breech presentation and other malpositions of the fetus can be explained by the abnormal interior of this type of uterus with its inability to accommodate the vertex properly in the lower pole at or near term. No explanation is given for the significant increase in malpresentation in the Group A uterus as compared to Group C and to all other groups.

Miscellaneous Operative Procedures Related to Type Anomaly.—

In this study there were 21 miscellaneous operative procedures employed; 11 in Group C, 6 in Group A, and 4 in all other groups. There were 9 manual removals of the placenta necessary, 5 of which occurred in Group C. The vaginal septum produced serious dystocia in 4 cases and required incision to allow for vaginal delivery. Four Pomeroy tubal ligations were performed. There were one dilatation and curettage, one appendectomy, one amniotomy, and one craniotomy performed. The latter was done on the aftercoming head following a version and extraction of a stillborn infant weighing over 4,000 grams. The infant had been in the transverse and an arm prolapsed following rupture of the membranes. There was also employed one manual dilatation of the cervix prior to a midforceps extraction because of an occult prolapse of the umbilical cord. This was in a case in Group C and a living infant was obtained.

Fetal Anomalies.—

Three fetal anomalies occurred in a total of 109 infants, an incidence of 2.8 per cent. This is much higher than the normal incidence and may be significant. One was a spastic paralysis of an infant in Group A delivered by low forceps who lived to 8½ years of age. Another was a metatarsus varus in an infant born by classical section because of a transverse presentation in a uterus with Group A anomaly at term. The third was a clubbed left foot in an infant born by assisted breech delivery in a uterus with Group A anomaly at thirty-nine weeks' gestation.

Indications for Cesarean Section.—

As noted previously in Table III, there were 41 cesarean sections in this series, a total of 38.0 per cent of all the deliveries. The various indications for these sections are listed in Table V.

TABLE V. INDICATIONS FOR CESAREAN SECTION IN RELATION TO PRESENTATION OF THE FETUS

INDICATION	VERTEX	BREECH	TRANS.	UNKNOWN
Pregnancy in double uterus	2	5	0	3
Multiple pregnancy	1	1*	0	0
Cephalopelvic disproportion	1	0	0	0
Obstruction by nonpregnant horn	3	2	0	2
Failure of trial of labor	1	2	0	1
Placenta previa	0	0	0	3
Other uterine bleeding	0	0	0	3
Congenital absence cervical canal	1	0	0	0
Uterine inertia	0	2	0	0
Intra-abdominal hemorrhage	1	0	0	0
Congenital heart disease	1	0	0	0
Pre-eclampsia	1	0	0	0
Repeat section	0	0	0	1
Prior removal nonpregnant horn	1	0	0	0
Sacculation pregnant horn anterior	0	1	0	0
Placenta accreta	0	0	0	1
Transverse presentation	0	0	1	0
Congenital pelvic deformity	1	0	0	0
Total	14	12	1	14

*One infant is not counted in twin pregnancy.

Comparison of Pregnancies in Normal Versus Double Uterus.—

The results of this study have been compared with the published figures of Fenton and Singh[2] and are listed in Table VI. We believe that the similar percentages obtained in both studies are quite significant and worthy of con-

siderable attention. Only certain discrepancies were noted to be present. We did not find as large a percentage of spontaneous abortions nor prematurely ruptured membranes but we had a much larger incidence of malpresentation and operative deliveries. They had a much higher incidence of postpartum atony and of dilatation and curettage for removal of retained secundines but had a practically identical incidence of postpartum hemorrhage. Practically all of our values exceeded the normal incidence as reported for the Sloane Hospital for Women and in this respect are in general agreement with the figures reported by Fenton and Singh.[2]

TABLE VI. COMPARISON OF PREGNANCIES IN NORMAL VERSUS DOUBLE UTERUS

	THIS STUDY	NORMAL*	ABNORMAL*
Corrected abortion rate	18.9%†	5.6%	16.5%
Viable birth rate	77.2	93.1	66.4
Term birth rate	57.5	85.0	56.1
Abruptio placentae	00.9	1.2	5.5
Other vaginal bleeding	2.8	1.9	7.4
Toxemia	3.7	14.2	11.1
Hydramnios	00.0	0.6	0.8
Malpresentation	28.7	3.9	17.5
Premature rupture of membranes	8.3	26.2	44.0
Premature labor	13.9	6.8	15.2
Precipitate labor	0.9	6.5	9.2
Intrapartum uterine inertia	5.5	3.2	20.3
Cervical dystocia	1.8	0.8	2.5
Operative deliveries	63.0	20.0	50.0
Postpartum atony	0.9	1.9	9.0
Postpartum hemorrhage	5.5	0.4	5.2
Dilatation and curettage for retained secundines	0.9	0.8	12.9
Corrected fetal mortality	8.7	0.9	8.5

*Normal and abnormal incidence from Table XI in Fenton and Singh.[2] Statistics of Sloane Hospital for Women from 1933-1942.

†7.1% were spontaneous abortions and 11.8% were caused by surgery.

The following 9 cases were managed in our prenatal clinic and represent an incidence of 0.3 per cent of our deliveries since Jan. 1, 1950. They will be reported here briefly (Table VII) as well as included in the over-all study.

CASE 1.—R. A., a 16-year-old primigravida, was admitted to our hospital with bleeding and cramping during the fourth month of pregnancy. Her last menstrual period was given as April 21, 1951, and her estimated date of confinement was calculated to be Jan. 28, 1952. All symptoms subsided on bed rest, sedation, and stilbestrol, and she was discharged to the prenatal clinic where the remainder of her prenatal course was uneventful except for one admission for false labor during the last trimester. True labor began on Jan. 18, 1952, with the fetus in the breech presentation. The contractions were of very poor quality and the first stage lasted twelve hours. During labor the fundus was noted to have an irregularity of contour interpreted by the examiner to represent an anomaly of the uterus. Spontaneous rupture of the membranes occurred during the second stage of labor with prolapse of the umbilical cord. Labor was terminated by delivery of a viable 6 pound, 12 ounce female infant as a double footling breech. Brisk third stage bleeding necessitated manual removal of the placenta. Exploration of the uterine cavity revealed the presence of uterus bicornis unicollis vagina simplex. The postpartum course was entirely uneventful. No hysterogram was obtained in the postpartum period.

CASE 2.—H. L., a 17-year-old gravida ii, para 0, abortus i, was first seen in our prenatal clinic on Dec. 12, 1950. The last menstrual period was given as June 1, 1950, and the estimated date of confinement was calculated to be March 7, 1951. The past obstetrical history revealed a spontaneous abortion at four and one-half months in 1949. Pelvic

examination revealed a complete vaginal septum and two cervices with a six-month pregnancy in the right horn of a double uterus plus adequate pelvic measurements. The prenatal course was complicated by a hypochromic anemia and an excessive weight gain. Transfusion was necessary during the eighth month. At term the fetus was found to be in breech presentation and delivery by cesarean section was deemed advisable. On Feb. 28, 1951, a low cervical cesarean section under spinal anesthesia was performed with delivery of a viable male infant from the right horn of a uterus duplex bicornis bicollis vagina septate. The postoperative course was entirely uncomplicated. No hysterograms were obtained in the postpartum period.

CASE 3.—E. J., a 30-year-old gravida iii, para ii, with an estimated date of confinement of Oct. 22, 1951, had a history of one previous stillbirth and one premature liveborn infant that failed to survive. The prenatal course was complicated by mild pre-eclampsia at term which responded to conservative therapy. Following response to treatment, labor was induced and terminated in an outlet forceps delivery of a viable 8 pound, 4 ounce male infant from left mentum anterior position following five hours of labor. Brisk bleeding following delivery necessitated manual removal of the placenta at which time a thick septum was found to extend from the fundus down to the lower uterine segment. A well-developed left horn permitting the introduction of a finger was found. The postpartum course was entirely uneventful. A hysterogram was done on Jan. 11, 1952, and revealed a uterus bicornis unicollis vagina simplex.

CASE 4.—S. W., a 25-year-old primigravida with a last menstrual period of Oct. 12, 1950, was first seen in our clinic on April 2, 1951. Examination revealed a pregnancy in the left horn of a uterus bicornis unicollis vagina septate. The prenatal course was without incident. Labor was normal and terminated in an outlet forceps delivery of a viable 6 pound, 7 ounce male infant in right occipitoanterior presentation. The vaginal septum was incised at time of delivery. The third stage was uncomplicated and the puerperium was normal. A hysterogram done on Feb. 8, 1952, revealed the presence of uterus unicornis unicollis vagina simplex. The opaque medium actually revealed only one-half of the uterine cavity but palpation confirmed the presence of the opposite half and it was deduced that this may be a rudimentary right horn in a uterus bicornis unicollis.

CASE 5.—D. H., a 27-year-old gravida iii, para i, abortus i, was referred to our clinic for management when fourteen weeks pregnant. Examination revealed a second-degree descensus uteri with a fourteen weeks' pregnancy contained in the left horn of a bicornate uterus. The uterus was then in second-degree retroversion and could not be reposited. The patient was placed on stilbestrol in accordance with the recommendations of Smith and Smith[73] and knee-chest exercises were advocated. Spontaneous complete abortion occurred at the sixteenth week of gestation. The postabortal period was entirely uneventful. A hysterogram performed after six weeks revealed a uterus bicornis unicollis.

CASE 6.—H. J., a 19-year-old primigravida with an estimated date of confinement of Sept. 23, 1951, was first seen in our clinic on Aug. 21, 1951. Record of previous prenatal care at the U. S. Naval Hospital, Charleston, S. C., indicated the patient had been hospitalized for threatened abortion during the third month of gestation. Examination revealed a uterus the size of an eight months' pregnancy and the presence of a double cervix. The fetus was found to be presenting by the breech. Labor began on Sept. 15, 1951, and terminated after eleven and one-half hours in spontaneous delivery of a viable 6 pound, 6 ounce female infant from the left side of a uterus duplex bicornis bicollis. The third stage was uncomplicated and the puerperium was without incident. A hysterogram was not obtained in this case as the patient was obliged to leave the immediate area prior to reporting back for her examination at six weeks post partum.

CASE 7.—B. B., an 18-year-old gravida ii, para i, with an estimated date of confinement of Oct. 10, 1951, had an uneventful prenatal course. She was admitted to the hospital on Oct. 8, 1951, for medical induction of labor which was unsuccessful. On Oct. 20,

TABLE VII. CASES OF PREGNANCY ASSOCIATED WITH CONGENITAL ANOMALIES OF THE UTERUS MANAGED AT THE U. S. NAVAL HOSPITAL, CAMP LEJEUNE, N. C.

DATA	CASE REPORTS								
	1	2	3	4	5	6	7	8	9
Patient	R. A.	H. L.	E. J.	S. W.	D. H.	H. J.	B. B.*	B. C.	M. T.†
Age (years)	16	17	30	25	27	19	18	35	28
Gravida	i	ii	iii	i	iii	i	ii	vi	i
Para	0	0	ii	0	i	0	i	i	0
E. D. C.	1/28/52	3/5/51	10/22/51	7/19/50	—	9/23/51	10/10/51	12/8/52	10/22/52
Prenatal course	Thr. Ab. S and S R	Hypochromic anemia	Mild preeclampsia	Normal	Thr. Ab.	Thr. Ab.	Normal	Prem. rupt. membranes	Chronic pyelitis
Pregnancy in weeks	40	39	40	40	16	39	40	34	38
Presentation and position	Breech	Breech	Left mentum anterior	Right occipitoanterior	—	Breech	Vertex	Vertex	Vertex
Method of delivery	Asst. breech	Low cerv. section	Outlet forceps	Outlet forceps	Spont. abort.	Asst. breech	Spont.	Low forceps	Low cerv. sect. V and E
Complications of labor and delivery	Postpartum atony Manual removal of placenta	Double uterus	Postpartum atony Manual removal of placenta	Dystocia (incision of septum)	—	None	None	None	None
Complications of puerperium	None	None	None	None	None	None	None	None	None
Type of uterine anomaly	Type C	Type A	Type C	Type C	Type C	Type A	Type C	Type C	Type G
Time anomaly diagnosed	Intrapartum	Prenatally	Intrapartum	Prenatally	Prenatally	Prenatally	Postnatally	Prenatally	Assumed prenatally
Condition of fetus	Living term, female, white 6-12 No fetal anomalies	Living term, male, white 5-13 No fetal anomalies	Living term, male, white 8-4 No fetal anomalies	Living term, male, white 6-7 No fetal anomalies	—	Living term, female, white 6-6 No fetal anomalies	Living term, male, white 5-14 No fetal anomalies	Living, premature, male, white 3 14 No fetal anomalies	Living term female, white 6-7 No fetal anomalies

*Laparotomy revealed rudimentary right horn.
†Laparotomy revealed congenital absence of left adnexa with uterus unicornis.

1951, a spontaneous vertex delivery of a viable 5 pound, 14 ounce normal male infant occurred after two hours of labor. The third stage was normal. The patient's past history revealed severe dysmenorrhea since the menarche. In 1948 an exploratory laparotomy had been performed and the right ovary and appendix removed with no improvement in the dysmenorrhea. After considerable investigation a hysterogram was performed in our clinic on July 25, 1952, which revealed the presence of uterus unicornis with a patent tube. A firm mass palpated alongside the uterus was believed to be a rudimentary horn. On Aug. 4, 1952, a pelvic laparotomy was done and the presence of the rudimentary horn was confirmed (Fig. 2). The appendix, right ovary, and tube had been previously removed. The rudimentary right horn was removed without incident. All menses since surgery have been free from pain.

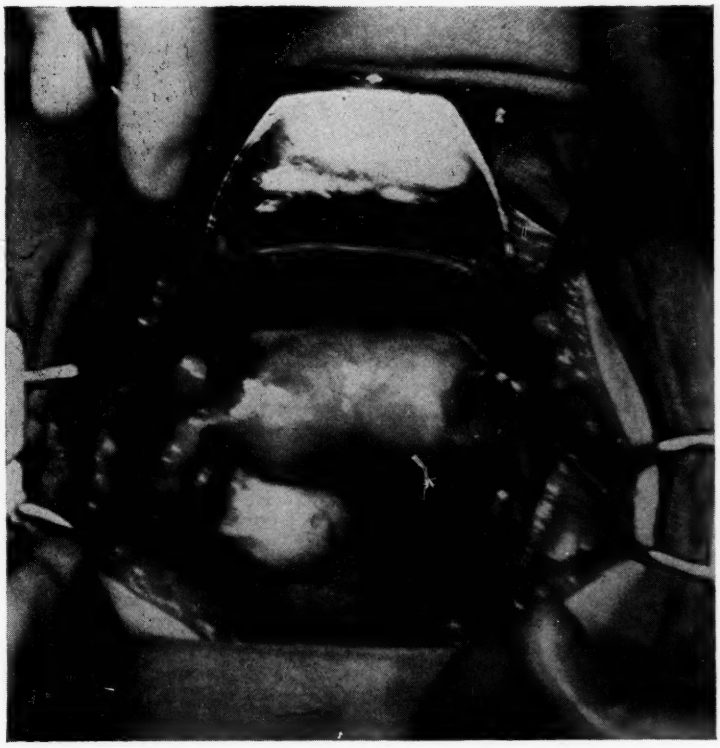

Fig. 2.—Uterus bicornis unicollis with rudimentary right horn (Case 7) revealed in situ at operation.

CASE 8.—B. C., a 35-year-old gravida vi, para i, was first seen in our clinic on July 12, 1952. Her last menstrual period was given as March 1, 1952, and the estimated date of confinement was calculated to be Dec. 8, 1952. Intermittent bleeding had been present for four weeks prior to the first visit. Examination revealed the presence of uterus bicornis unicollis with a four months' gestation in the left cornu. The patient was started on stilbestrol therapy in accordance with the recommendations of Smith and Smith.[73] Past history revealed a laparotomy in 1941 for vaginal bleeding and a "pelvic tumor." At surgery the patient was found to have a uterus bicornis unicollis with a four weeks' pregnancy in one horn. Spontaneous abortion followed the operation. In 1945 a viable 5 pound, 4 ounce male was delivered spontaneously at eight months' gestation. Spontaneous abortions at two and one-half to three months' duration occurred in 1949, 1950, and 1952. The course of this pregnancy had been uneventful until about seven and one-half months when premature rupture of the membranes occurred. Labor ensued and was

accompanied by moderate vaginal bleeding. Following a relatively short labor a living 3 pound, 14 ounce male infant in apparently good condition was delivered with elective low forceps and a left mediolateral episiotomy. The third stage was uneventful. Manual exploration of the uterine cavity revealed a well-developed right cornu and the left horn which had contained the pregnancy. The postpartum course was without incident.

Fig. 3.—Pelvic deformity and pyelogram revealing agenesis of left kidney in Case 9.

Fig. 4.—Uterus unicornis and agenesis of left ovary, tube, and supporting ligaments (Case 9) revealed in situ at cesarean section.

CASE 9.—M. T., a 28-year-old primigravida, was first seen in our clinic when five months pregnant. Numerous congenital anomalies were noted on examination, namely:

absence of left kidney, marked left lumbar scoliosis, and spina bifida occulta. Atrophy of the left leg and thigh had resulted from disuse and necessitated the wearing of a brace. The pelvis was asymmetrical with an obliquely elliptical inlet. The left ilium articulated directly with the fifth lumbar vertebra. The left ala of the sacrum was markedly underdeveloped (Fig. 3). Urinary incontinence had been constantly present until the age of 14 when a sympathectomy was performed. Self-catheterization three times daily had been necessary since the sympathectomy. This resulted in repeated urinary tract infections requiring almost constant ingestion of some antibiotic or sulfonamide drug. A laminectomy and spinal fusion were performed in 1934 and sensation was noted in the left leg for the first time. Intravenous pyelography revealed a marked hydronephrosis of the right kidney and congenital absence of the left. The prenatal course was complicated by repeated bouts of pyelitis requiring hospitalization. On Oct. 8, 1952, at thirty-eight weeks' gestation, a low cervical cesarean section was performed under 2 per cent procaine local anesthesia because of the congenital deformity of the pelvis. As anticipated, a uterus unicornis without the left adnexal structures was found (Fig. 4). A living 6 pound, 7 ounce female infant was delivered by version and extraction from a vertex presentation without incident. A Pomeroy type tubal ligation was then performed. The postpartum course was essentially uneventful and the patient was discharged with her baby on the ninth postoperative day. A hysterosalpingogram was done after the six weeks post partum visit and exhibited the outline of a uterus unicornis.

Comment

One hundred eighteen individual cases of pregnancy complicated by some form of uterine anomaly were collected from the English and French literature during the period 1930 through 1951 and along with 9 cases of our own were subjected to a careful analysis in order to determine the proper method of management in each type of presentation in relation to the type of anomaly present and to obtain the lowest possible fetal mortality. It was noted that the condition occurred much more frequently than was previously thought and its incidence increased in direct proportion to the diagnostic acumen of the individual or group concerned. The incidence of antenatal diagnosis was better than half but would be much improved if hysterosalpingography were resorted to in all cases of sterility,[72] habitual abortion, premature labor, premature rupture of the membranes, and unexplained stillbirth. The greatest number of anomalies in our study occurred in Groups A and C and as a result should have produced no acute problem in antepartum diagnosis. The 127 patients had 275 pregnancies, an average of 2.16 pregnancies per patient. This effectively eliminates any lack of fertility in the general group. In 127 individuals, there were 98, or 77.2 per cent, viable births. When 25 premature births are subtracted from this figure, we have a term viable birth rate of 57.5 per cent which is definitely lower than normal but compares favorably with that reported by the Sloane Hospital Group.[2] There occurred in our study the equivalent of 24 abortions, an incidence of 18.9 per cent. Nine, or 7.1 per cent, were spontaneous, and the remaining 15, or 11.8 per cent, were produced inadvertently by surgery. The largest number of pregnancies lost prior to viability occurred in Group C and this fact is of definite significance. There was a total of 109 infants born in this study with 14 fetal deaths, an incidence of 12.8 per cent. However, when this figure is corrected for 5 infants as previously noted, the fetal mortality becomes 8.3 per cent, and this compares

very favorably with the reported results of Fenton and Singh.[2] When the fetal deaths were analyzed from the standpoint of uterine anomaly present, it was noted that 11 deaths, or 23.9 per cent, occurred in Group C. The 5 deaths for which the figures were corrected also occurred in Group C, and we feel this fact to be significant. When the fetal deaths were studied in relation to the presentation, it was noted that 4 were vertex, one was transverse, and 4 were unknown. Nothing of statistical value could be obtained from this phase of the study. However, when the fetal mortality was considered along with the type of delivery and with the type of anomaly, it was quite evident that operative delivery appeared to increase the fetal mortality, but this finding could have occurred by chance in this study. Only 5.0 per cent of 40 nonoperative deliveries resulted in the death of the fetus while version and extraction and various types of cesarean section were responsible for the remainder. Our study is unusual, perhaps, in that no deaths can be attributed to breech delivery or extraction. Certainly this is not the usual pattern in the management of pregnancies in a normally developed uterus. We cannot offer any logical explanation for this paradox. There were in this study 63.0 per cent operative deliveries of which 41 cases, or 38.0 per cent, were cesarean sections. It is felt by our group that this incidence is too high and reflects the lack of faith in vaginal delivery by the majority of physicians doing obstetrics. It is quite evident that spontaneous delivery of preferably a vertex presentation will result in a lower fetal mortality if no cephalopelvic disproportion is present and is, therefore, the procedure of choice. When the indications for cesarean section were critically scrutinized in each case, we felt that perhaps most of the operations may have been justified except for the 10 cases done just because of the presence of a double uterus. This indication may be acceptable in a breech presentation with borderline measurements and certainly in a transverse, but otherwise should not be considered. Oddly enough, we noted only one repeat section in our entire study. The indication with the next highest incidence was obstruction from the nonpregnant horn, and we feel it is certainly acceptable. The remainder, as noted in Table V, were done for sharply defined legitimate indications. The analysis of the fetal weights in relation to the fetal mortality and uterine anomaly present, as noted previously, did not reveal much information of statistical importance. It was considered highly significant that the 3 maternal deaths and 23.7 per cent of the total morbidity occurred in Group C. The complications of labor were increased over the normal incidence with premature labor the highest but divided evenly between Groups A and C. Retained placenta and premature rupture of the membranes shared third place and obstruction of labor by the nonpregnant horn occupied second place with an incidence of 12 occurrences, 8 of which were found in Group A. The complication of pregnancy that was noted most frequently in our study was malpresentation. There were 34 abnormal positions of the fetus. Certainly this is a significant finding and should cause one to consider the presence of a uterine anomaly whenever confronted by other than a vertex presentation. There were 9 manual removals of the placenta, 5 of which were done in Group C. This complication of retained

placenta requiring manual removal apparently occurs more frequently in this type of uterus and must of necessity be anticipated. The 3 fetal anomalies in this study all occurred in Group A and gave rise to the rather high incidence of 2.8 per cent, a rather significant figure. The comparison of results as noted in Table VI is rather striking. In almost all instances our results are in accord with those of Fenton and Singh[2] with the exception of our higher incidence of operative delivery and their higher incidence of premature rupture of the membranes. We had no cases of hydramnios and a very low incidence of toxemia. The results of both studies were well in excess of the published normals, however, and confirm certain ideas regarding management of such cases as well-established facts.

Conclusions

1. An analysis of one hundred twenty-seven cases of pregnancy associated with various congenital anomalies of the uterus has been presented.

2. Nine additional cases of our own have been included in the analysis and added to the literature.

3. The incidence of spontaneous abortion was not found to be increased over the normal in the cases in this study.

4. The fetal mortality was found to be twice as high in the group of patients delivered by operative means but this difference is not statistically significant.

5. It appears from this study, although not statistically evident, that spontaneous delivery of preferably a vertex presentation offers the best opportunity for a live baby in this type of uterus.

6. The types of double uterus noted under A, B, C, F, and G in Fig. 1 should offer no difficulty in antenatal diagnosis if the condition is constantly kept in mind when a malpresentation occurs.

7. Palpation of the pregnant uterus during a contraction will in many instances give one an inkling of the true condition present as the irregular contour of the fundus will become much more apparent.

8. Hysterosalpingography is recommended in all cases of sterility,[72] habitual abortion, premature labor, premature rupture of the membranes, and in cases of unexplained stillbirth, as a means of detecting certain anomalies listed in Fig. 1 under Groups D and E.

9. From the results of this study, it was apparent that malpresentation, premature rupture of the membranes, and premature labor are to be anticipated in pregnancies associated with a double uterus. As a measure designed possibly to improve fetal salvage, it is recommended that all such cases be placed on stilbestrol therapy in accordance with the recommendations of Smith and Smith.[73]

10. There was a significant increase in fetal anomalies in double-uterus pregnancies.

11. Pregnancy in a double uterus per se is not a valid indication for bilateral tubal ligation nor therapeutic abortion.

12. Surgical removal of an obstructing nonpregnant horn near term is contraindicated as it will increase the hazard of rupture of the uterus during labor and carries the same risk as a myomectomy or previous classical cesarean section scar.[74] Such patients should be subjected to elective low cervical cesarean section as soon as the diagnosis is evident.

13. Elective cesarean section has no place in the management of pregnancy in a double uterus except in the presence of definite obstetrical indications that would prompt a similar decision in pregnancy in a normally developed uterus or in the event of dystocia produced by an obstructing nonpregnant horn.

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TREATMENT OF HYPEREMESIS GRAVIDARUM WITH CORTISONE

I. Fetal Results

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THE cause of nausea and vomiting that so frequently accompany pregnancies that are otherwise normal has been the subject of much speculation and controversy. The pathological processes sucessively proposed as responsible for this condition virtually span the known causes of human disease. A relative adrenocortical insufficiency was first proposed by Kemp[1] in 1932 and has been studied and subscribed to by many other investigators.[2-7] Vomiting of pregnancy has been treated with adrenal cortical extract, occasionally in massive doses, with relatively good results. In view of these favorable reports of the use of this extract and the present availability of the pure synthesized adrenal hormone, cortisone, the clinical trial of minimal doses of cortisone in the therapy of vomiting of pregnancy is logical.

I[8] recently treated a number of hyperemesis patients with minimal doses of cortisone (or ACTH), the rationale being the previously mentioned theory of adrenocortical insufficiency. The theory, briefly, is as follows: Many cases of vomiting of pregnancy are possibly due to a *secondary* adrenocortical insufficiency. Hyperemesis usually occurs in the first three months of pregnancy, during a period in which the pregnancy is hormonally dependent upon the anterior pituitary. In some patients there occurs a relative (temporary) deficiency in the adrenocorticotropic fraction of the anterior pituitary. (It has even been postulated that ACTH and the gonadotropic hormone are formed by the same cell.) The resultant adrenal insufficiency produces the hyperemesis, the mechanism being similar to that of Addison's disease, which, indeed, a full-blown case of hyperemesis frequently resembles in symptoms, signs, and laboratory findings. When the placenta assumes the principal hormonal obligations of of pregnancy, the vomiting usually ceases, with or without, or sometimes in spite of, the treatment.

Twenty-nine consecutive cases of nausea and vomiting of pregnancy severe enough to require treatment were treated with cortisone. Seven of these were considered severe enough to be classified as hyperemesis. Results were rather startling. Twenty-three of the patients had a complete remission of symptoms within 36 hours with no recurrence. Five had cessation of symptoms within 36 hours with only occasional recurrence. One responded and had no further weight loss, but after being free of symptoms for several days had recurrence of vomiting averaging one to two episodes daily for some time. Cortisone was withdrawn from the first seven patients with recurrence of symptoms within 72 hours. To remove the psychogenic element the next 22 consecutive patients

were each controlled with a placebo. When the patient had been free of symptoms for 24 to 72 hours, a placebo was substituted for the cortisone. Twenty of these 22 patients had recurrence of symptoms. Two patients, who both had milder cases and were in the third month of pregnancy, had no recurrence. Cortisone and the placebo were interchanged at irregular intervals. To remove the element of prejudice, one of the authors dispensed the medication while the other took the histories and talked with the patients. The historian never knew whether the patient was on cortisone or a placebo. The results were not correlated until some time afterward. The total daily dosage of cortisone varied from 25 mg. to 75 mg., with one patient receiving 100 mg. for two days. The total time the patients were receiving cortisone (or a placebo) ranged from 5 to 64 days, averaging about three weeks. The stage of pregnancy at which cortisone was begun varied from 4 to 12 weeks. There was no apparent immediate deleterious effect on any patient. Cortisone was used for the bulk of the patients due to the relative scarcity of ACTH at the time this work was done. In 2 of the patients, however, the cortisone was interchanged with ACTH (usually 10 mg. a day) with no detectable difference. Since it is the primary purpose of this paper to report the fetal statistics, detailed analysis and discussion of the clinical results of this study will not be given here (but will appear in another paper).

TABLE I

CASE NUMBER	PERIOD OF TREATMENT (WEEKS OF GESTATION)	DOSAGE RANGE (MG.)	TOTAL DOSAGE (MG.)	FETAL STATISTICS
1	8- 9 12-19	25-100	788	Apparently normal term baby
2	7-11	25-50	850	Apparently normal term baby
3	6-10	25	675	Apparently normal term baby
4	6- 8	25	200	Apparently normal term baby
5	6-13	25-50	987	Apparently normal term baby
6	6-16	25-50	1,987	Apparently normal term baby
7	7-11	25-50	870	Coarctation of aorta; baby died
8	7-11	50	1,150	Apparently normal term baby
9	6-11	50	737 (25 ACTH)	Apparently normal term baby
10	8- 9	50	250	Apparently normal term baby
11	7-11	25	262 (27 ACTH)	Apparently normal term baby
12	7- 8	37.5	375	Apparently normal term baby
13	11-12	50	350	Undescended testicles; baby died
14	7-11	25-50	1,037	Apparently normal term baby
15	9-13	50	1,200	Apparently normal term baby
16	4-10	50	1,250	Apparently normal term baby
17	8-11	25	500	Apparently normal term baby
18	6-11	25-75	1,500	Apparently normal 2.25 kg. baby
19	5- 7	50	350	Apparently normal term baby
20	6-13	25-62.5	1,312	Apparently normal term baby
21	6- 9	50	500	Patient moved; lost contact
22	12-17	25-50	1,462	Clubfoot
23	8- 9	25	125	Apparently normal term baby
24	6- 9	25-50	700	Apparently normal term baby
25	11-12	50	350	Apparently normal term baby
26	8-11	25-37.5	525	Apparently normal term baby (Cataract found at 2½ months)
27	6- 9	25-50	612	Apparently normal term baby
28	9-10	25	125	Patient moved; lost contact
29	6- 8	50	350	Apparently normal term baby

Two of the patients have moved away, and contact has been lost. Of the remaining 27, 24 delivered apparently normal fetuses. Two of them weighed 2.25 kilograms; the remaining 25 weighed in excess of 2.75 kilograms. There was one baby with coarctation of the aorta who lived five days, one with a clubfoot, and one with undescended testicles that died of unknown cause at two days (Table I).

CASE 1.—The patient, a 16-year-old white primigravida with moderate vomiting, was started on cortisone at the beginning of the seventh week of pregnancy. She was given 50 mg. daily for four days with cessation of symptoms. She did not return for 11 days. At the end of this time she had had a marked recurrence of symptoms and was given 50 mg. a day for a week, following which the cortisone was gradually withdrawn. She received a total of 870 mg. of cortisone. She was delivered of a 3,175 gram female infant who lived five days with atrioventricular dissociation and supraventricular rhythm. Autopsy showed coarctation of the aorta. The heart showed no abnormality other than enlargement characteristically seen in association with coarctation. Of interest is the history that the patient's mother had congenital heart disease of an unknown type.

CASE 2.—A 19-year-old white primigravida with severe hyperemesis, who had been treated with most of the usual medications but had not responded, was started on cortisone during the twelfth week of pregnancy. The daily dosage varied from 25 to 50 mg. with a total dosage of 1.5 Gm. over a period of 38 days. She was delivered of a 3,000 gram female infant with a severe calcaneovalgus deformity of the right foot and marked limitation of plantar flexion.

CASE 3.—A 17-year-old white primigravida with moderate vomiting, who did not respond to pyridoxine, was given 50 mg. of cortisone a day for one week beginning in the twelfth week of pregnancy. She was delivered of a 2,250 gram male infant at 36 weeks. The baby died of an unexplained cause on the third day. The autopsy was negative except for undescended testicles.

Each baby was carefully examined after birth by the same physician. One baby, who was found to be normal by careful physical examination at birth, was found to have a cataract of the left eye at 2½ months.

In this brief clinical report no attempt will be made to discuss fully the possible relationship between the cortisone and the congenital defects. The following embryological relationships, however, may be of significance.

Case 1.—Coarctation of the Aorta.—The development of the heart and great vessels is usually complete during, or at the end of, the sixth week. This patient first received cortisone during the seventh week.

Case 2.—Clubfoot.—There are two theories as to the etiology of clubfoot.[9] The more frequently cited is the "mechanical theory," i.e., it is due to malposition of the foot in utero. The other theory attributes clubfoot to an arrest of embryological development between the fourth and the ninth weeks of gestation, the abnormality being the more severe the earlier the arrest occurs. This patient received cortisone initially during the twelfth week of pregnancy.

Case 3.—Undescended Testicles.—The testicles normally descend between the seventh and ninth months of gestation.[10]

It is our purpose to present this report as briefly and as quickly as possible for the information and evaluation of all those interested in the critical problem of the administration of cortisone to the pregnant patient.

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THE USE OF BANTHINE IN NAUSEA AND VOMITING OF PREGNANCY*

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THE study of nausea and vomiting of pregnancy is an interesting subject, especially when the older texts are reviewed and their early methods are analyzed. Many theories and treatments had been used which were later discarded. This seems to be a never-ending process.

Lusk[49] in his textbook of 1886, states, "There are few known therapeutic agents which have not at one time or another been essayed as remedies for nausea and vomiting of pregnancy. Some of them have even enjoyed for a time high repute as specifics, but the sobering effect of experience has invariably served to dispel illusive hopes, the most successful of them proving uncertain, and of benefit to only a limited class of patients." This statement is still quite appropriate.

The mere listing of remedies would fill a small volume and would no doubt be the source of much interesting speculation. About 70 years ago correction of retroversion of the uterus, painting of a cervical erosion with silver nitrate, ether or faradic current to the pit of the stomach, inhalation of oxygen, ice-cold effervescent drinks, dry champagne, subnitrate of bismuth and oxylate of cerium, nux vomica, Fowler's solution, morphine, chloral hydrate, and pepsin were used with varying success.

Twenty years later, a list compiled by Williams[66] is little changed. He adds moderate dilatation of the cervical canal by means of a steel dilator or a small pack, and large quantities of normal saline for hydration.

Treatment as we know it today began to evolve in the early 1920's. Foremost was the use of insulin,[1, 32, 40, 42, 47, 60] ovarian extracts,[9] such as corpus luteum,[37, 68] and of sodium bicarbonate[14] to combat acidosis. The foundation of these methods rests upon diet—nothing by mouth for 24 to 48 hours, then frequent small feedings, intravenous 5 to 10 per cent glucose solutions,[12, 19, 33, 61] and sedation,[52] principally by sodium bromide.[7] Various other methods in vogue then were thyroid extract,[13] Adrenalin,[14] placental substance,[11] roentgen-ray treatments,[58] cerium oxylate, and serum of women who spontaneously recovered from toxemia.

More recently, attention to diet, 5 per cent intravenous glucose solutions, and sedation have remained the basis of treatment to which have been added such medications as adrenal cortex,[17, 34, 41, 45] ovarian extracts, parathyroid extracts,[59] Lugol's solution,[22] thiamine chloride and pyridoxine,[17, 34, 36, 43, 64, 65, 67] ascorbic acid,[16, 29] liver extract,[28, 54] testosterone,[20] and husband's blood.[38]

*Read at a meeting of the Pittsburgh Academy of Medicine, May 12, 1953.

The most recent literature continues to expand the number of drugs used. Polyamine anion exchange resins,[24] Dramamine,[8, 10] vitamin K combined with vitamin C,[51, 53] antihistaminics,[18, 23] Dexedrine,[2] stilbestrol,[4, 23] and ACTH[5] are now being tried.

From the beginning, neurosis[35, 55] has been considered as playing a large factor in the etiology, and most authors have stressed the approach to the patient from this aspect. The treatment has varied from hypnosis[46] at one extreme to the advice of Atlee[3]—"The vomit bowl is kept away from the patient and she is told that, if she must vomit, she can do so in bed."

Two years ago, we selected Banthine (methantheline bromide) for treatment of nausea and vomiting of pregnancy, because of its pronounced parasympathetic and sympathetic ganglionic blocking effects resulting in reduced gastric secretion and tone and reduced gastrointestinal motility.

Procedure

Five obstetricians and three general practitioners were selected to treat their cases of nausea and vomiting of pregnancy with Banthine as we directed. Their prior beliefs as to treatment were not investigated in order that a fairer evaluation might be obtained.

Twenty-five mg. of Banthine was given every 8 hours the first day. If this was unsuccessful, 50 mg. was given every 8 hours the second day; if still unsuccessful, 50 mg. was given every sixth hour until the symptoms were relieved. There were many complaints of a bitter taste so that later an enteric-coated tablet was used with good results. Fifty cases were collected. After one year each physician was again asked what he thought of the value of Banthine.

Results

Thirty-seven (74 per cent) patients were relieved completely of their symptoms, while there were twelve (24 per cent) failures. One case was considered equivocal, for the first week produced no results, but after a week's rest the second attempt proved satisfactory. Of the twelve failures (Table I), corpus luteum and vitamin B relieved one patient and failed in one; Dramamine relieved three and failed in one; phenobarbital relieved two; tincture of hyoscyamus helped one; pyridoxine and thiamine chloride helped two and failed in one.

Banthine relieved only a small number relatively quickly, for it usually required seven days and occasionally somewhat longer to obtain a successful result. There were a few of those relieved on whom Dramamine, corpus luteum, or pyridoxine and thiamine chloride had previously failed.

As we mentioned before, some patients complained of the bitter taste which was remedied with an enteric-coated tablet. Vomiting or dryness of the mucous membranes was another occasional side effect, but was due in every instance to overdosage.

One year later these same physicians were asked their opinions on the effectiveness of Banthine in relieving nausea and vomiting of pregnancy (Table II). Six of the eight physicians are still using Banthine and are generally less enthusiastic than previously, but maintain that it was of value in a certain group of patients. The remaining two discontinued its use because they were dissatisfied with the results.

TABLE I. EFFECT OF SUBSEQUENT TREATMENT OF 12 CASES IN WHICH BANTHINE WAS A FAILURE

TREATED WITH	SATISFACTORILY	UNSATISFACTORILY
Corpus luteum and vitamin B	1	1
Dramamine	3	1
Phenobarbital	2	
Tr. hyoscyamus	1	
Pyridoxine and thiamine hydrochloride	2	1
Total	9	3

TABLE II. OPINIONS OF 8 PHYSICIANS ON THE VALUE OF BANTHINE IN NAUSEA AND VOMITING OF PREGNANCY

PHYSICIANS	USING BANTHINE	USING BANTHINE EXCLUSIVELY	USING BANTHINE MOST FREQUENTLY	METHOD OF TREATMENT INDIVIDUALIZED	OTHER METHODS
1.	Yes	No	No	Yes	Dramamine, sedation, vitamins B_1 and B_6
2.	No	—	—	Yes	Dramamine, sedation, antispasmodics
3.	Yes	Yes	Yes	No	
4.	Yes	No	No	Yes	Dramamine, sedation, Dexamyl, Dexedrine, vitamin B_6
5.	No	—	—	No	Vitamin B complex and folic acid intravenously, sedation
6.	Yes	No	Yes	No	Vitamin B complex intramuscularly, sedation, Pavatrine, Emetrol
7.	Yes	No	No	Yes	Vitamin B_6 intravenously, sedation
8.	Yes	No	Equal	Yes	Dramamine, sedation, vitamin B_6

Comment

Undoubtedly neurosis must be of major concern and these patients should be handled with insight into their problems. This does not mean that other methods are superfluous. Diet and supportive treatment are the backbone of our procedure. During the past year we have been using, in addition to 5 per cent glucose intravenously, a solution of 5 per cent alcohol in 5 per cent glucose with vitamin B complex added. Probably in no other disease are there so many treatments with so many reported good results and yet with a complete answer so far away.

One of us (A. W. C.) observed that the better results occurred in those who have had a history of previous gastric upset or pylorospasm. We wish to suggest, therefore, that those patients who have nausea and vomiting should not be treated as a group, but as individuals. Possibly a patient with a history of motion sickness would respond more often to Dramamine, a nervous or excitable one to phenobarbital, a thin, undernourished, pale person to vitamins, a person who has experienced hormonal imbalance to thyroid, stilbestrol, or corpus luteum, one troubled with states of depression to Dexedrine or Dexamyl or, on occasion, a combination of those mentioned may be of value. We believe, with this in mind, that Banthine does have a place in the treatment of nausea and vomiting of pregnancy but should be used in selected cases. Newer antisecretory drugs may give similar results and probably will be given a trial by others soon.[44]

Summary

1. Seventy-four per cent of the fifty patients treated with Banthine responded satisfactorily.

2. We believe that patients with nausea and vomiting of pregnancy should be individualized and treated accordingly as to history and symptomatology.

3. Generally, the physicians interviewed were less enthusiastic than one year ago, but were of the opinion that Banthine should be considered when treating nausea and vomiting of pregnancy.

We wish to thank G. D. Searle & Company, for the supply of Banthine.

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DESCENT OF THE PRESENTING PART IN PREGNANCY AND LABOR

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TEXTBOOK descriptions of the mechanism by which the fetal head descends in late pregnancy, and of the phenomenon of "lightening" appear to be based on the classical paper on the subject by Rudolph (1937). This paper has rightly deserved the attention paid to it, for the available evidence was carefully collected and patiently examined. Nevertheless, it is felt that Rudolph's explanation is not entirely satisfying and the present essay is an attempt to produce a modified hypothesis which fits all the facts.

Rudolph's Hypothesis

Briefly, Rudolph attributed the phenomenon of lightening to two mechanisms: one, a falling forward of the uterine fundus due to a reflex relaxation of the abdominal muscles, the second, "is due to the final physiological phase in the formation of the lower uterine segment which passively allows the presenting part to descend into the pelvic cavity." He stated that in this second mechanism there is "no retraction or thickening of the upper uterine segment," although he mentioned that there is "ample evidence in the literature for a decrease in the distance between the cervix and the fundus uteri in the prone position."

Objections to Rudolph's Hypothesis

It is well known that, whereas, in the absence of disproportion or other obstruction, the fetal head usually enters the pelvis in the primigravida in late pregnancy, in the multigravida the descent may not occur until labor begins, or indeed until labor is well advanced and the membranes ruptured. If the descent of the fetal head were purely a passive matter depending on the formation of the lower segment, descent of the head should occur more readily in the woman whose pelvic soft parts have been dilated by previous labors. Moreover, this failure of the presenting part to engage in multiparas is not necessarily due to a lax abdominal wall, for in many cases the presenting part is high and mobile despite adequate tone in the abdominal muscles. In these cases the whole uterus, as well as its contents, gives the impression of being freely mobile and but loosely anchored to the pelvis.

A further inconsistency in Rudolph's theory is his denial that the upper segment retracts in pregnancy. If there is elongation of the lower uterine segment (Rudolph's evidence for this is strong) and if the total length of the uterus from cervix to fundus is the same or smaller after "lightening" (as Rudolph says it is), then it follows by simple arithmetic that the upper segment must have become shorter. Surely, when it is known that the uterus

is actively contracting and relaxing, is it not more reasonable to assume that this shortening is an active process, viz., retraction? In any case, to postulate that an expansion of the lower segment occurs from about 2 cm. to more than 6 cm. (to quote Rudolph's own figures), entirely by a process of relaxation, seems less plausible than to suppose that the upper segment has undergone retraction, the lower segment having been expanded by this activity.

The Uterine Attachments

Let us digress for a moment to consider by what means the uterus is anchored. The parametrium is attached fanlike along the sides of the uterus, lower segment, and cervix, sweeping outward to the side walls of the pelvis as well as backward and downward to the sacrum as the uterosacral ligaments. The uterus is also anchored through its lower segment by continuation of the vaginal musculofascial layer onto the uterus. Finally, the hypertrophied round ligaments have some effect in fixing the uterus. All these attachments act like guy ropes in mooring the uterus to the pelvis and they have an important function in parturition, which, although obvious, does not receive general recognition in the description of normal labor as given in the textbooks, other than by DeLee (1947). Without these moorings which provide countertraction the uterus could not propel the fetus through the pelvis.

The Modified Hypothesis

The upper uterine segment, by virtue of its properties of contraction and retraction, has two functions. The first is to draw the lower segment up over the fetal ovoid as a tight vest might be stripped off a small boy; during this process the cervical os dilates and the width of the lower segment increases. The second duty is to drive the baby through the birth canal. These two processes do not necessarily run side by side. In the primigravida, as a rule, the early retraction of late pregnancy immediately makes taut the uterine moorings, which are as yet unstrained by labor, and the presenting part descends into the pelvis (provided no obstruction exists). This descent runs parallel with the taking-up of the cervix and expansion of the lower segment which are effected by the same early retraction. In the multigravida the uterine moorings may have been stretched by previous labors, for they have provided the countertraction for the full force of the upper segment in labor. In these cases there is much slack to be taken up by retraction of the upper segment before countertraction is exerted for the baby to be driven down. Thus it is that in the woman who has had previous babies the retraction of the upper segment may have to produce considerable dilatation of the cervix, even perhaps full dilatation, before the uterus and the baby lose their mobility and descent of the presenting part occurs.

The short answer, then, to the question, "Why does the presenting part often not engage before term in the multigravida?" is "Because the uterine moorings may be too slack as a result of previous labors."

Practical Applications of These Concepts

If it be remembered in a case with a mobile presenting part that this is held to the brim by the uterine attachments, it follows that the strain on these moorings cannot be greater than the force required to displace the presenting part upward at vaginal examination and this includes consideration of the strain across the lower segment, which is anchored as explained above. So long, therefore, as the presenting part is still mobile or easily displaced, the strain on the lower segment cannot be great.

This test is of help in the management of the multigravida with a contracted pelvis who may occasionally reach full dilatation while the head remains free. If the head is easily displaced, the slack in the uterine moorings has not yet been taken up and there can be no obstruction present. If the head cannot be displaced, then the lower segment may be becoming dangerously stretched and rupture may be imminent; in fact, forcible dislodgment of the presenting part may produce that catastrophe!

Similar considerations come into force when the obstetrician is faced with the problem of a woman with minor pelvic contraction and a history of a previous cesarean section, not preceded by adequate trial of labor. Is it dangerous to allow labor to start in such a case? Let us assume that we are not averse to allowing vaginal delivery after a previous lower segment cesarean section in cases where the pelvis is normal. Then it can be argued that so long as the presenting part is not clamped firmly into the brim, there should be no objection to allowing labor to begin, even if there be a contracted pelvis. The strain on the lower segment in the first instance is only that caused by pulling it up over the fetal ovoid and this will be the same regardless of the presence or absence of disproportion. Once, however, the presenting part begins to bite the brim and is held there by some force, this force is the measure of the possible strain on the lower segment through which the uterus is anchored. Unless the head has passed the brim at that stage, the risk of rupture of the uterus will increase above that present in patients without a contracted pelvis.

Summary

1. Some criticisms are raised of the usual explanation of the mechanism by which descent of the fetal head in pregnancy is effected. The usual textbook account does not explain satisfactorily the frequent failure of the head to enter the pelvis before labor in multigravidas.

2. Arguments are given for the existence of some retraction of the upper segment in late pregnancy and for the importance of this in producing descent of the fetal head.

3. A brief account of the uterine moorings is given, showing that they provide countertraction by which the upper segment is enabled to drive the fetus down the birth canal. The frequent occurrence of a high presenting part at term in multigravidas can be attributed to the slackness in these moorings produced by previous labors.

4. Consideration is given to the role of the uterine attachments in causing strain on the lower segment in labor. The bearing of this on the management of cases of contracted pelvis in the multigravida or after previous lower segment cesarean section is discussed.

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ETIOLOGY AND MANAGEMENT OF IDIOPATHIC PELVIC PAIN*

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THERE is a cause for all pain and the use of the word "idiopathic" means we are still searching for the cause. It also means that we have ruled out all obvious causes such as tumor, acute infections, chronic infections, ureteral stone, and prolapses. There have been many attempts to explain pelvic pain, as is seen in Table I. Chronic metritis is one explanation because the uterus is often enlarged and boggy and shows thickening of the blood vessel walls upon microscopic examination. Chronic salpingitis is another explanation and is based upon the fallacious theory that pain must result from infection, even if there is no obvious infection. Chronic appendicitis is still a popular explanation of pelvic pain, if the pain is limited to the right side of the pelvis. Adhesions are blamed, after surgery fails to relieve the pain. Taylor[1] advocated the congestion theory, and more recently Duncan and Taylor[2] have observed that there is a strong nervous element present in these patients. They suggest that psychoanalysis may be necessary to uncover the hidden cause.

TABLE I. THEORIES OF ETIOLOGY OF PELVIC PAIN

1. Chronic metritis
2. Chronic salpingitis
3. Chronic appendicitis
4. Adhesions
5. Congestion
6. Psychoneurosis
7. Ovarian dysfunction

For the past twelve years I have been treating pelvic pain on the assumption that it is due to ovarian dysfunction. Table II shows the signs and symptoms that are associated with pelvic pain in the ovarian dysfunction syndrome. They are not all present in every patient. I have noted[3, 4] as has Taylor[2] that often one or both ovaries are cystic, that menorrhagia or metrorrhagia may be present, and that many of these patients are tense and nervous. I have been unable to decide whether nervousness causes the ovarian dysfunction or whether the reverse is true. Simple instruction in proper living corrects most of this nervousness and I have found very few patients who seem to have serious, deep-seated personality disorders. Many patients overindulge in coffee and cigarettes, which aggravate their nervousness. A mild sedative, such as phenobarbital, helps these patients control their emotions. Such treatment is often necessary after the treatment for the ovarian dysfunction. Sedation alone has been ineffectual in controlling the pain. High-dosage estrogen therapy, diethylstilbestrol 5.0 mg. or conjugated estrogen (Premarin) 5.0 mg. daily for 20 days, has been quite successful in relieving pain.

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TABLE II. SYNDROME OF OVARIAN DYSFUNCTION

1. Pelvic pain
2. Menorrhagia
3. Metrorrhagia
4. Cystic ovaries
5. Tender ovaries
6. Tender uterus
7. Dyspareunia
8. Infertility
9. Nervous exhaustion

None of the theories of the cause of pelvic pain can be proved by therapeutic test, except that of ovarian dysfunction. Certainly, removal of the uterus in "chronic metritis" does not relieve the pain, unless the ovaries are also removed. Chronic salpingitis is often diagnosed when the temperature, leukocyte count, blood sedimentation rate, and tubal appearance are normal. Salpingectomy done in these patients does not relieve pain unless ovarian surgery is also performed. Removal of the appendix in cases of "chronic appendicitis" is followed by recurrence of the pain in a large percentage of cases.[5] Lysis of adhesions may relieve pain, if the ovaries are freed so they may function normally. If lysis fails, the explanation of the failure is that the lysis produced new adhesions. Taylor, the chief advocate of the congestion theory, admits there is no treatment for congestion. The following 91 patients with idiopathic pelvic pain were treated on the assumption that the pain was due to ovarian dysfunction and the cases are reviewed to show the results of such treatment.

Material

The patients in this study were seen by me in my private practice. Pelvic pain, either unilateral, bilateral, or of low midline type, was present as a chief complaint in all. Slight pelvic pain or discomfort, not given by the patient as a reason for seeking medical care, was not included. Most of the patients were ambulatory, but a very few had such severe pain that they were hospitalized. This was done so that serious intra-abdominal pathology could be ruled out and so that the supine position could help relieve the ovarian pain. All patients were followed by subsequent examinations by me or by follow-up letter. Patients seen once only, who could not be reached for follow-up, are not included because there is no assurance that they took the prescribed treatment.

Method

Each patient had a complete history taken and a physical examination done. This included examination of the entire body, ophthalmoscopic and otoscopic examination, bimanual pelvic and speculum examination, rectal palpation, urinalysis and hemoglobin determination, plus any special studies that might be indicated. Any organic pathology that might have a bearing upon the cause of pelvic pain was ruled out. Pelvic examination confirms the diagnosis of ovarian dysfunction. The uterus is normal or slightly enlarged and is often tender. One or both ovaries are always moderately to exquisitely tender.

The first treatment given these patients was estrogen in large doses in an attempt to correct the ovarian dysfunction. Most patients received diethylstilbestrol orally, 5.0 mg. daily for 20 days, after the method of Karnaky.[6] Many received pyridoxine intravenously, 150 mg. with the first dose, to reduce nausea, as previously reported.[7] Some received conjugated estrogen (Premarin) orally 5.0 mg. daily for 20 days, instead of diethylstilbestrol. Some patients received more than one course of estrogen, especially if the first course gave them complete but temporary relief. Many patients received phenobarbital gr. ¼ three times daily orally along with instructions for rest, relaxation, the avoidance of tension, and reduction of the intemperate use of coffee and tobacco. This treatment of the nervous element was given before or after the course of estrogens. In no case was it sufficient in itself to relieve completely the pelvic pain. In many cases it was needed after the estrogens because the patient was still tired and nervous and requested relief of these symptoms also.

Since this method of estrogen therapy would appear to depend upon an ovary capable of being stimulated to function normally, I have used it chiefly in women under 40 years of age.

When the patient failed to have the pain relieved by estrogens or when the relief was so transient that she wearied of continued therapy and wished for more permanent relief, she was treated surgically. The most conservative operation that is successful is the puncture of the multiple small cysts that are usually found in these ovaries. An alternate method is to resect the ovaries partially. Neither of these operations necessarily gives permanent relief. Complete and permanent relief can be assured if bilateral oophorectomy is done, accompanied by hysterectomy and salpingectomy. This is radical treatment and is reserved for those patients who are almost incapacitated by their pain and who have been under treatment for months or years.

Results

Table III shows the result of administering estrogen to women with pelvic pain. Seventy-nine of 91 patients were pain free by the end of the second month. The estrogen was given for 20 days. Many patients had pain relief within a few days and most were relieved by the end of the third week. The pelvic organs in these were not tender at this time. A few still had pain at the end of the third week, but, if the uterus and ovaries were no longer tender to palpation, the patient could be promised pain relief within another four weeks without further treatment. Of the 79 patients who were relieved of pain by the original course of estrogen, 52 were still comfortable when last contacted 4 months to 12 years later. In most cases the interval was about 2 to 5 years from their first treatment. Some of these 52 women had returned for a second course of treatment but were pain free at the time of this survey.

TABLE III. RESULTS AFTER TREATMENT OF PELVIC PAIN WITH ESTROGENS

	1-2 MONTHS AFTER TREATMENT	
NO. PATIENTS	PAIN RELIEVED	PAIN CONTINUED
91	79	12
	4 MONTHS TO 12 YEARS AFTER TREATMENT	
	RELIEF CONTINUED	PAIN RECURRED
79	52	12

Table IV analyzes the patients who did not respond to estrogen therapy. Twelve of the original 91 women were not relieved at the end of the three-week treatment period and their ovaries remained tender to palpation. Four patients decided to tolerate their pain when surgery was suggested as the next treatment. One patient became pain free when she divorced a brutal husband and remarried happily. The remaining seven were relieved by surgical procedures. A salpingo-oophorectomy was done in one with endometriosis, and a bilateral salpingo-oophorectomy in one with chronic salpingitis. Three were treated by multiple puncture of the ovarian cysts although it was realized that this does not effect a permanent cure. Two had total abdominal hysterectomy and bilateral salpingo-oophorectomy to assure permanent pain relief.

TABLE IV. SUBSEQUENT HISTORY OF PATIENTS WHOSE PELVIC PAIN WAS UNRELIEVED BY ESTROGENS

	EARLY FAILURES	LATE RECURRENCES
Pain relieved by other treatment	8	7
Cystic ovaries punctured	3	1
Uterus, tubes, ovaries removed	2	4
Ovary removed—endometriosis	1	1
Tubes removed—chronic salpingitis	1	0
Divorce, remarriage	1	0
Uterus suspended, adhesions (elsewhere)	0	1
No further treatment. Refused surgery	4	5
Total	12	12

Twelve of the original 79 who were relieved by estrogen had recurrence of their pain which did not respond again to estrogen. Of these, 5 refused surgery, one had an endometrial cyst of the ovary removed, one had multiple cysts of the ovaries punctured, and 4 had total abdominal hysterectomy and bilateral salpingo-oophorectomy. All those operated upon were relieved of their pain. One patient was operated upon elsewhere and had a uterine suspension and lysis of adhesions done with relief of pain.

Comment

The concept of ovarian dysfunction as the basic cause of "idiopathic" pelvic pain gives us a rational approach to the problem of relieving this pain. Large-dose estrogen therapy relieves most patients very quickly. (I believe this is accomplished by depressing the hypophysis, which in turn permits the ovaries to rest for the duration of the treatment.) If this fails, the ovary with multiple small cysts may be resected, as is done by Stein and Leventhal, or it may be merely punctured. This is useful in younger patients whose desire for children will compensate for the possibility that further surgery may be necessary. When all else fails the surgeon can be assured that removal of both ovaries will relieve all of this type pain. The tubes and uterus are also removed in such cases because they have no further value and are a potential danger. It is wise to ask patients before surgery if they require relief from their pain or are merely fearful that they have cancer or other

serious disease. Nine patients in this study refused surgery although they claimed their pain was not relieved by medical management.

The pathology found at the operating table is disappointing until we remember that ovarian dysfunction is a *functional* disease rather than one showing gross pathology. Some patients, but not all, have small polycystic ovaries. A few have early endometriosis and the theory has been advanced that endometriosis may be due to ovarian dysfunction.

Summary and Conclusions

1. Theories of the etiology of pelvic pain without demonstrable pelvic pathology are reviewed.

2. The concept of ovarian dysfunction as the cause of this type of pain is presented.

3. The pelvic findings of tender uterus and ovaries are presented as typical of this condition.

4. Ninety-one patients with pelvic pain were treated with large doses of estrogen for 20 days.

5. Seventy-nine patients were relieved immediately and 52 patients remained pain free.

6. Fourteen patients were treated surgically and pain relief resulted.

7. Estrogen therapy should be used first in treating idiopathic pelvic pain.

8. Pain persisting after estrogen therapy may be relieved by ovarian surgery. Resection, cyst puncture, or oophorectomy may be done, depending upon the patient's age, parity, and other factors.

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THE VOLUME OF THE AMNIOTIC FLUID IN THE EARLY MONTHS OF PREGNANCY

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DESPITE the steadily growing literature on the chemistry and physiology of the human amniotic fluid there are still very few data recorded regarding its volume, especially in the early stages of pregnancy. This lack of information is frequently a handicap to the interpretation of certain abortion specimens, particularly those in which the volume of the amniotic fluid appears out of proportion to the stage of development reached by the embryo; in such cases it is difficult to be certain whether the amount of fluid is normal or abnormal.

The following study on the volumes of amniotic fluid in intact gestation sacs from early pregnancies, was undertaken in an attempt to increase our scant knowledge of this subject.

Materials and Methods

The material consisted of intact gestation sacs and was obtained in the Province of Manitoba, Canada, principally from the cities of Winnipeg and St. Boniface. Each specimen was preserved in 10 per cent formalin and examined about forty-eight hours after abortion or operation had occurred. The intact sac was measured and weighed, then, with the specimen held over a filter funnel, the sac was incised and the amniotic fluid measured by collection in a graduated cylinder. The color of the fluid, its degree of opacity or translucency, and the presence or absence of sediment were noted. The embryo was measured (crown-rump length), weighed (provided maceration did not interfere with handling), and examined for anomalies. The umbilical cord and the sac wall were also inspected for abnormalities; a segment of the latter was removed in each case and examined microscopically.

In all, 476 specimens were examined, and of these it was possible to determine the volume of the amniotic fluid in 66 (Table I). Of the latter, 62 were from intrauterine, and 4 were from extrauterine gestations. Of the former group, 9 were obtained by hysterotomy, the remaining 53 being aborted naturally per vaginam.

For purposes of classification, a specimen from an intrauterine pregnancy was considered "normal" if it conformed with the following: (1) no abnormality of the embryo, umbilical cord, placenta, or membranes; (2) no maceration or compression of the embryo; (3) the amniotic fluid was not gelatinous nor did it contain heavy sediment; (4) the actual menstrual age of the specimen did not exceed the estimated menstrual age by more than one and one-half weeks.

The *actual menstrual age* was reckoned from the first day of the last normal menstrual period to the time of delivery of the specimen. The *estimated menstrual age* was obtained by adding two weeks to the fertilization age of the embryo, the latter being calculated from the crown-rump length by means of a conversion table devised by Patten.[1]

As a result of this classification, 14 specimens from intrauterine pregnancies were classed as "normal." The 4 specimens from extrauterine gestations were considered as a separate group.

Observations

The data gathered for the 66 specimens are summarized in Table I. The volume of the amniotic fluid obtained from each of the intrauterine gestations is shown graphically in Fig. 1, that from the four extrauterine gestations, in Fig. 2, *B*. The smallest volume of amniotic fluid collected was 1.2 ml., the largest, 500 ml. The actual menstrual age of the youngest specimen was 6.5 weeks, of the oldest, twenty-eight weeks. The crown-rump lengths of the embryos ranged from 2.5 mm. to 179 mm.

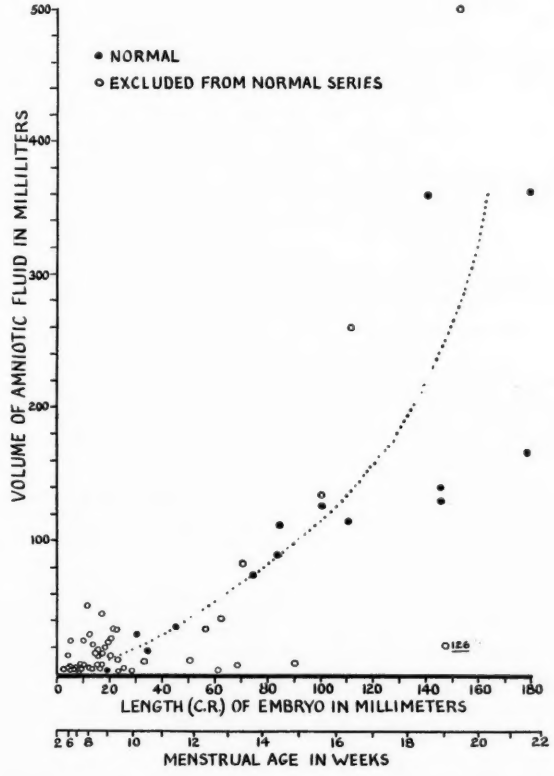

Fig. 1.—Shows the relation of the volume of the amniotic fluid to the crown-rump length of the embryo, and the estimated menstrual age of the pregnancy, in sixty-two intrauterine gestations. Fourteen normal specimens are distinguished from the other members of the series. The underlined figure in the lower right corner indicates the number of a specimen. The curve was fitted by inspection.

A. Intrauterine Gestations.—

1. "Normal" Specimens.—The distribution of the volumes of the amniotic fluid from the fourteen "normal" specimens is shown in Fig. 1.

TABLE I

NO.	EMBRYO LENGTH (MM.)	EMBRYO WEIGHT (GRAMS)	AMNIOTIC FLUID VOLUME (ML.)	AMNIOTIC FLUID COLOR†	MENSTRUAL AGE* ESTIMATED	MENSTRUAL AGE* ACTUAL	NO.	EMBRYO LENGTH (MM.)	EMBRYO WEIGHT (GRAMS)	AMNIOTIC FLUID VOLUME (ML.)	AMNIOTIC FLUID COLOR†	MENSTRUAL AGE* ESTIMATED	MENSTRUAL AGE* ACTUAL
7	17.0	–	45.0	Cl.	9.0	11.5	252	23.0	1.5	2.0	–	9.5	?
10n‡	145.0	195.0	140.0	Y. Cl.	19.0	19.0	253	70.0	36.3	83.0	B. Op.	13.5	21.0
29	5.0	–	4.5	Y. Cl.	6.0	6.5	254	15.0	–	7.0	Y Op.	8.5	?
37	25.0	–	5.0	Y. Op.	10.0	12.0	261	16.5	–	8.0	–	8.5	?
39n§	30.0	–	30.0	Y. Cl.	10.0	10.5	271n	110.0	133.8	115.0	Y Op.	16.5	17.5
55	10.5	1.2	7.0	B. Op.	7.5	11.0	277	19.0	–	24.0	–	9.0	14.0
72	17.0	–	16.0	Y. Cl.	9.0	13.0	292	20.0	–	14.0	–	9.0	14.0
81	6.0	–	3.0	Y. Cl.	6.5	10.0	294	9.0	–	3.0	Y. Cl.	7.5	?
83	100.0	–	134.0	B. Op.	15.5	20.0	303	4.0	–	15.0	–	6.0	12.5
98	14.5	–	16.0	Y. Op.	8.0	11.5	305	7.0	–	3.0	B. Cl.	7.0	?
100‖	20.0	1.3	4.3	Cl.	9.0	?	314	5.5	–	25.0	–	6.0	15.0
104	68.0	54.0	7.0	B. Op.	16.0	?	325	22.5	–	34.0	B. Op.	9.5	13.0
106n	84.0	49.0	112.0	Y. Cl.	14.5	14.5	329	4.5	6.0	5.0	–	6.0	10.0
111	8.0	–	1.4	–	7.0	9.5	330	10.0	–	25.0	B. Cl.	7.5	17.0
112n	145.0	248.0	130.0	Y. Cl.	19.0	18.0	333	15.5	–	15.0	B. Cl.	9.5	?
113	56.0	45.0	34.4	B. Op.	12.0	25.0	339	2.5	–	3.4	Cl.	5.0	11.0
116‖	15.0	–	1.2	B. Op.	8.5	8.5	342n§	83.0	43.8	90.0	B. Cl.	14.0	13.0
119	61.0	17.0	3.0	B. Gel.	13.0	13.0	352	11.0	–	51.0	Cl.	8.0	12.5
126	147.0	350.0	22.0	B. Op.	19.0	20.0	369n	178.0	510.0	165.0	–	21.5	23.0
131	50.0	10.5	11.0	B. Op.	12.0	16.0	376	23.0	–	11.0	–	9.5	13.0
141n§	100.0	73.0	127.0	Y. Cl.	15.5	16.0	383	18.0	–	20.0	B. Cl.	9.0	11.5
142	116.0	169.5	260.0	B. Op.	16.5	20.0	384§	152.0	306.0	500.0	Y. Op.	19.0	24.0
147	13.0	–	4.4	B. Op.	8.0	11.0	396n§	45.0	19.0	37.0	–	11.5	12.0
148	4.0	–	6.0	B. Cl.	6.0	13.0	397	9.0	–	8.0	–	7.0	12.0
151n§	34.0	5.0	18.0	B. Op.	10.5	?	400	28.0	–	2.0	B. Op.	10.0	28.0
152n§	74.0	38.2	75.0	Y. Op.	13.5	?	409n§	19.0	–	3.2	Cl.	9.0	9.5
156	15.0	–	19.0	Y. Op.	8.5	13.0	419	7.0	–	30.0	B. Cl.	7.0	12.5
160	90.0	65.2	8.0	B. Op.	15.0	?	432	13.5	–	21.0	B. Cl.	8.0	10.0
162	33.0	5.3	10.0	Y. Op.	10.5	15.0	442	62.0	17.4	42.0	–	13.0	?
168n	179.0	520.0	362.0	Y. Cl.	21.5	23.0	453	21.5	–	35.0	Y. Op.	9.0	?
178	20.0	–	27.0	Y. Op.	9.0	12.0	458	12.0	–	5.0	Cl.	8.0	?
243n§	140.0	210.0	360.0	Y. Cl.	18.5	14.0	468	16.5	–	3.5	–	8.5	?
245‖	12.0	–	0.5	Y. Cl.	8.0	8.0	493‖	22.0	15.0	5.0	Cl.	9.5	?

*The menstrual age is given in weeks.
†Cl. = clear; Op. = opaque; Gel. = gelatinous; Y. = yellow; B. = brown.
‡n = normal specimen.
§Specimen obtained by hysterotomy.
‖Specimen from tubal pregnancy.

In this group, the amniotic fluid was usually yellow in color and translucent (Table I); however, in the youngest specimen (No. 409, 19 mm.) it was crystal clear, and in a slightly older specimen (No. 151, 34 mm.), it was opaque and brown but without sediment; in No. 342 (83 mm.) it was translucent and brown. In none of the 14 specimens was the fluid of a muddy or gelatinous nature.

Eight of the specimens in this group were obtained by hysterotomy.

2. Specimens Excluded from the "Normal" Series.—Figs. 1 and 2, *A* show that the fluid volumes of the 48 specimens of this section arrange themselves, relative to the normal series, into three principal groups: Group I, in which the fluid volumes lie above and to the left of those of the normal group; Group II, in which the fluid volumes lie close to or among those of the normal group; and Group III, in which the fluid volumes lie to the right and below those of the normal group.

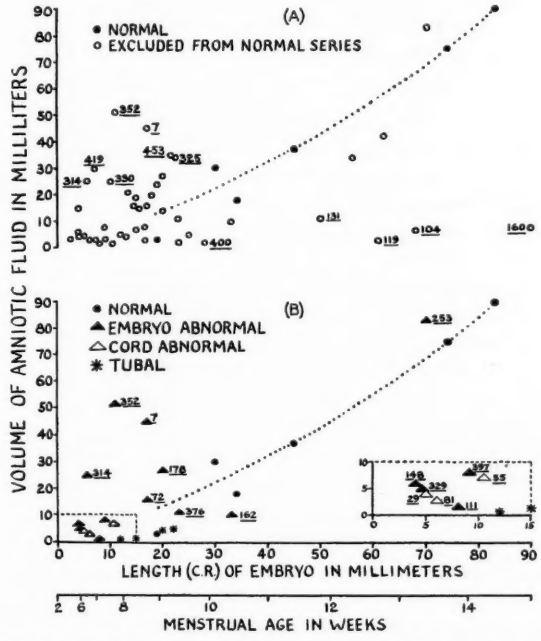

Fig. 2.—*A*, Shows the lower left corner of Fig. 1, in detail; *B*, shows the distribution of the volumes of the amniotic fluid in the abnormal and tubal specimens. In both *A* and *B* the curve was fitted by inspection. The underlined figures are the numbers of specimens.

Group I: There are 7 specimens in this group but one (No. 453) will not be discussed on account of the inadequacy of the maternal history.

No. 7: The embryo measured 17 mm. and showed cerebral herniation in the region of the vertex, and an ectodermal defect of the anterior thoracic wall. The disparity between the estimated and actual menstrual ages was 2.5 weeks. The amniotic fluid was crystal clear and amounted to 45 ml., a volume which might be anticipated in a normal pregnancy of the same menstrual age.

Nos. 325 and 330: Both specimens contained embryos which were normal in appearance. In each, the amount of amniotic fluid was more than expected for the estimated menstrual age but less than anticipated for the actual menstrual age. The umbilical cord, in both cases, was attached to the sac wall in such a way that the umbilical vessels had to course for some distance

in the wall before reaching the presumptive placental site; the appearance was similar to that of velamentous insertion of the cord as occasionally seen in older specimens.

No. 352: The embryo measured 11 mm. and showed iniencephaly; the amniotic fluid amounted to 51 ml. and was crystal clear. The disparity between the estimated and actual menstrual ages was 4.5 weeks. As in No. 7, the fluid volume was in keeping with the actual menstrual age of the pregnancy.

No. 419: The embryo measured 7 mm. and was of normal appearance. The volume of the amniotic fluid was 30 ml., an amount too large for the estimated, and too small for the actual menstrual age of the specimen, as was the case in Nos. 325 and 330. The findings were essentially similar in No. 314, except that the difference between the estimated and actual menstrual ages was marked, 9 weeks.

Group II: With the exception of No. 29, all the 35 specimens in this group had fluid volumes, which, although in keeping with the estimated menstrual age, were less, in some cases much less, than expected for the actual menstrual age. In this group were 12 of the 15 specimens in which there was abnormality of the embryo or the umbilical cord; these will be considered later.

Group III: There were 6 specimens in this group:

No. 119: The embryo measured 61 mm. and was of normal appearance. The amniotic fluid was of gelatinous consistency and had a volume of 3 ml., much less than anticipated for either the estimated or the actual menstrual ages; the latter were in agreement. The specimen was aborted eleven days after emergency appendectomy.

No. 126: The fetus measured 147 mm. and showed clubbing of both feet, and only one umbilical artery in the cord. The amniotic fluid, brown in color and opaque but devoid of sediment, amounted to 22 ml., a volume less than expected for either the estimated or the actual menstrual ages (Fig. 1). Since the latter differed by only one week, and the fetus was not macerated, it is probable that fetal death and abortion occurred about the same time. The maternal history stated that the uterus was studded with fibroids.

No. 400: The embryo measured 28 mm. and, although macerated, showed no abnormality of form. It was accompanied by 2 ml. of muddy-brown amniotic fluid, an amount much less than anticipated for either the estimated or the actual menstrual ages.

Nos. 104, 131, AND 160: These presented features similar to No. 400; in No. 131, the disparity between the estimated and the actual menstrual ages was 4 weeks; the maternal history was not available for the other two specimens.

3. Abnormal Specimens.—Fifteen of the 62 specimens showed abnormality of either the embryo or the umbilical cord; the volume of the amniotic fluid which accompanied each is shown in Fig. 2, *B*. Specimens with abnormal embryos were: No. 7, cerebral herniation in the region of the vertex, and an ectodermal defect of the anterior thoracic wall; No. 72, cerebral herniation in the region of the vertex; No. 111, monster; No. 148, stunted embryo; No. 162, polydactylism; No. 178, iniencephaly and spina bifida; No. 253, amniotic adhesions and multiple anomalies; No. 314, stunted embryo; No. 329, cystic outgrowth of the thoracic wall; No. 352, iniencephaly; No. 376, spina bifida; and No. 397, stunted embryo. Abnormality of the umbilical cord was a feature of: No. 29, reduction of the umbilical cord to a filmy membrane and absence of the cord vessels; No. 55, marked expansion of the middle portion of the cord; and No. 81, in which the appearances were similar to those in No. 29.

Three of the above specimens belonged to Group I, Nos. 7, 314, and 352, and the remainder to Group II, as described in the previous section.

In Nos. 7 and 352, the amniotic fluid was crystal clear; in the others, it varied in appearance but was never gelatinous or muddy.

B. Extrauterine Gestations.—

Four of the 66 specimens were from tubal pregnancies, Nos. 100, 116, 245, and 493 (Table I). The volume of the amniotic fluid which accompanied each is shown in Fig. 2, *B;* in No. 116 the fluid was opaque, in the others, translucent. The menstrual history was available for Nos. 116 and 245; in both, the estimated and actual menstrual ages were in agreement. All the embryos appeared normal.

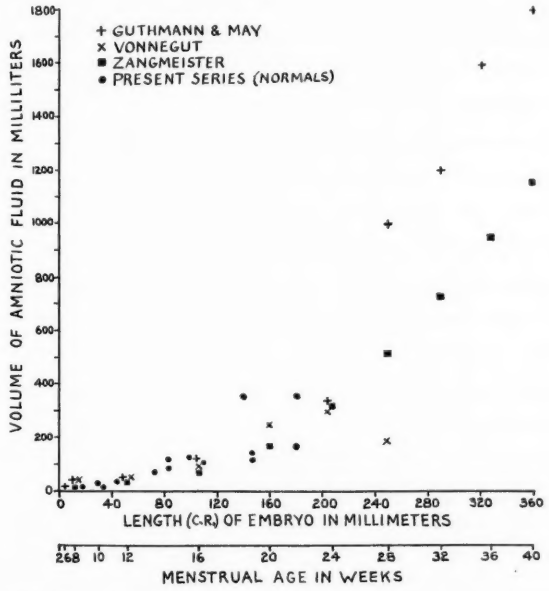

Fig. 3.—Shows the amniotic fluid volumes of the fourteen normal specimens along with the findings of Zangmeister, Vonnegut, and Guthmann and May, for comparison.

Comment

1. Consideration of the Normal Series.—

The volumes of the amniotic fluid in each of the fourteen specimens of the normal series are shown graphically in Fig. 1. For comparison, the same series is shown in Fig. 3 with the findings of Zangmeister,[2] Vonnegut,[3] and Guthmann and May.[4] The volumes of Zangmeister and Vonnegut are monthly averages, those of the latter being the results of observations on 33 specimens, 5 of which were obtained by operation. The data of Guthmann and May were collected from a study of 9 specimens, all procured by operation. The distribution of the volumes of the amniotic fluid in specimens of all four series is fairly similar until approximately the sixteenth week of pregnancy, after which differences become more marked. The pattern of geometric progression, suggested by the distribution of the volumes of the amniotic fluid in the normal series (Fig. 1), of this study, is probably not often maintained throughout the remainder of pregnancy; indeed, the findings of Guthmann and May indicate that it ultimately takes on a logistic form. In

Zangmeister's series this trend is less obvious, the curve adopting a pattern somewhat midway between exponential and logistic. Considerable individual variations in the form of the curve doubtless occur.

In animals such as the guinea pig (Ibsen[5]) and the cat (Wislocki[6]), the volume of the amniotic fluid gradually rises until term, whereas in the rabbit (Lell[7]), after a period of rise, it undergoes almost complete resorption a few days before the end of pregnancy. Intermediate patterns are found in the sheep (Patten[8]), in which the volume of the amniotic fluid, after increasing to a maximum, remains almost constant until term; and in the sow (Wislocki) and hamster (Purdy and Hillman[9]), in which a degree of terminal resorption occurs. In man, the pattern most frequently followed is probably that exemplified by the sheep, sow, and hamster, although it is possible that, under certain circumstances, more extreme patterns resembling those of the cat and the rabbit may occur.

Several specimens of the normal series of the present study, and of the three other series referred to earlier, were obtained by operation, either hysterotomy or hysterectomy. It is generally considered that such specimens are more likely to be normal than those which are aborted naturally per vaginam, and, in the majority of cases, this is probably true. Termination of pregnancy by operation, however, is almost invariably undertaken on account of some maternal pathological state which, conceivably, may have affected the development of the embryo, and perhaps also the volume of the amniotic fluid. For such reasons, specimens obtained by operation should be subjected to as careful scrutiny and consideration as those aborted naturally. It is felt that a useful check may be made by comparing the estimated and the actual menstrual ages of each specimen, as has been done in this study, and rejecting from a normal category those in which the difference is unduly great. In the present investigation, one hysterotomy specimen (No. 384) was excluded from the normal series for such a reason (Table I).

2. Variations in the Volume of the Amniotic Fluid.—

In Nos. 7 and 352 of Group I, the volume of the amniotic fluid, while excessive for the estimated, was in keeping with the actual menstrual age of the pregnancy, as judged from the distribution of the fluid volumes of the normal series. It is considered that the relatively large amount of fluid present in each case is not related to the abnormalities of the embryos, but to the increased capacity of the gestation sac from (a) the reduced rate of growth of the embryo, and (b) the approximately normal rate of enlargement of the uterus. It will be appreciated, however, that, in such specimens, although the volume of the fluid is that which might be expected in a normal pregnancy of similar menstrual age, the capacity of the gestation sac will actually be less, on account of the smaller size of the contained embryo.

In Nos. 325 and 330 of the same group, it is not improbable that circulatory disturbance, as a result of the way in which the umbilical vessels traverse the sac wall, may have had some effect on the volume of the amniotic

fluid. The possible significance of velamentous insertion of the cord on the development of the embryo has been mentioned elsewhere (Monie[10]).

In all the specimens of Group I, with the exception of Nos. 7 and 352, the volume of the fluid, while larger than expected for the estimated menstrual age, was smaller than anticipated for the actual menstrual age. It is likely that, in these specimens, the amniotic fluid has been partly resorbed in the time which has elapsed between the death of the embryo and the delivery of the specimen.

The findings in Group II specimens, in which the fluid volume was that expected for the estimated, but less than that anticipated for the actual menstrual age, may be accounted for in one of two ways: (a) the volume of the amniotic fluid and the size of the uterus have remained unaltered since the time of death of the embryo; or (b) the amount of amniotic fluid was originally greater but has undergone partial resorption. It is not possible to say which of these is the more probable.

In each of the specimens in Group III, the volume of the amniotic fluid was less than anticipated for either the estimated or the actual menstrual age, and it would appear that much of the fluid had undergone resorption prior to abortion; No. 126, however, was an exception. In the latter, in view of the absence of maceration, and the close agreement of the estimated and actual menstrual ages, the amount of fluid collected at the time of examination was probably close to that accompanying the fetus when death occurred. In this case, it would appear that fibroids, preventing normal uterine expansion, resulted in an unusually small volume of amniotic fluid and associated deformities of the fetus. The limitation of uterine expansion as a possible cause of oligohydramnios has been discussed by Taussig.[11]

Specimen No. 119, aborted eleven days after emergency appendectomy, is of interest as it possibly indicates the relative rapidity with which the resorption of the amniotic fluid may occur under certain circumstances. It is impossible to estimate, however, how much resorption took place prior to, or after, fetal death.

3. Abnormal Specimens.—

Most of the specimens in which there was abnormality of the embryo or the umbilical cord were found in Group II. In the case of 5 specimens in which the embryos showed closure defects, such as spina bifida, the amount of the amniotic fluid was not excessive for the actual menstrual age of the pregnancy. Also, there is no evidence to indicate that in any specimen of the series the volume of the amniotic fluid was attributable to abnormality of the embryo. The significance of the findings in Nos. 325 and 330 has already been discussed.

4. Color of the Amniotic Fluid.—

Except in the few cases in which the amniotic fluid was muddy, due to the disintegration of the embryo, there was no apparent relationship between the color of the fluid and abnormality of the specimen. Generally, the fluid

was yellow in color and transparent; however, in some abnormal specimens it was crystal clear, and in some normal specimens it was brown and opaque.

Although the appearance of the fluid was judged after preservation, the findings are in agreement with recorded observations on unpreserved material.

5. Tubal Gestations.—

The volumes of the amniotic fluid in the 4 specimens obtained by operation for tubal pregnancy are shown in Fig. 2, *B*. Their distribution relative to the normal series might suggest that in tubal pregnancy the volume of the amniotic fluid is less than in intrauterine pregnancy of similar duration.

Considering the findings in the material of the present study, it is felt that (a) the size of the embryo or fetus, and (b) the degree of expansion permitted the gestation sac by the uterus (or uterine tube) are important factors in determining the volume of the amniotic fluid at any given time.

Although this investigation was undertaken on preserved material, the findings do not differ greatly from those in unpreserved specimens (Fig. 3). In any case, since the material received by the pathologist for examination is almost invariably preserved, data for such specimens would seem equally desirable.

Much more information is required about the changes in the volume of the amniotic fluid during pregnancy, especially in the first and second trimesters; it is unfortunate that this subject has been neglected for so long.

Summary

1. The volume of the amniotic fluid in each of sixty-six intact gestation sacs from the first and second trimesters of pregnancy is considered in relation to the length of the embryo, the estimated and actual menstrual ages of the pregnancy, and, in certain cases, to aspects of the maternal history. Sixty-two of the specimens were from intrauterine pregnancies; four were from tubal gestations.

2. The distribution of the volumes of the amniotic fluid in fourteen "normal" specimens follows the pattern of an exponential curve but it is unlikely that such would be maintained for the remainder of pregnancy.

3. No relationship between abnormality of the embryo and the volume or the color of the amniotic fluid could be determined.

4. In the specimens from tubal pregnancies, the volume of the amniotic fluid appeared less than in intrauterine pregnancies of equivalent duration.

5. The size of the embryo and the degree of expansion of the uterus (or the uterine tube) are considered important factors in determining the volume of the amniotic fluid at a given stage of pregnancy.

6. The need for more observations on the volume of the amniotic fluid in the early stages of pregnancy is stressed.

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HYSTEROSALPINGOGRAPHY STUDIES FOLLOWING ECTOPIC PREGNANCY

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IN THE review of a series of 70 ectopic pregnancies operated upon at our institution, it was noted that 7, or 10 per cent, were repeat operations for the same disease of the residual tube. When one considers that 14 of the 63 patients had sterilizing procedures at the time of the first laparotomy (usually resection of the uninvolved tube for obvious salpingitis) our percentage incidence of repeat ectopic tubal pregnancy is 14.3 per cent.

Our incidence of ectopic pregnancy in general when compared with several other representative series (Table I) does not seem out of line. The reported incidence of repeat ectopic tubal pregnancy in other series, however, varies from 1.73 per cent to 6.6 per cent[1, 2] (Table II), and here our figure is unexpectedly high. This high incidence along with the high incidence of pelvic inflammatory disease in our clinic (14.5 per cent of revisits and 16.1 per cent of new patients) led us to the study reported here. We wished to determine by available means the fate of the remaining tube following surgery as well as to establish the role that pelvic inflammatory disease plays in the etiology of ectopic pregnancy. Another interesting question which arose during our studies was whether or not intraperitoneal blood, with its subsequent clotting, organization, and possible formation of peritubal adhesions, predisposes the patient to another tubal pregnancy.

TABLE I. INCIDENCE OF ECTOPIC PREGNANCY IN REPRESENTATIVE SERIES

AUTHOR	DATE REPORTED	NO. OF CASES	RATIO OF ECTOPIC TO INTRAUTERINE PREGNANCIES	PERCENTAGE OF GYNECOLOGIC ADMISSIONS
Jarcho[1]	1949 (1934-1947)	173	1:69	1.44
Nucci[2]	1946 (1934-1944)	150	1:212	1.46
Farell[3]	1943 (1931-1942)	75	1:45	1.30
Thornton[4]	1947 (1928-1946)	67	1:67	—
Cleveland City Hospital	1952 (4 years)	70	1:95	3.78

Material and Methods

Due to the difficulty encountered in appraising either the clinical history or previous outpatient diagnosis of pelvic inflammatory disease we have studied

a comparatively recent group of patients whose availability for follow-up and repeat pelvic examination was naturally greater. This would also lessen the possibility of intercurrent pelvic infection, that is, between surgery and our study.

TABLE II. INCIDENCE OF RECURRENT ECTOPIC PREGNANCY

AUTHOR	DATE REPORTED	NO. OF CASES	INCIDENCE OF RECURRENT ECTOPIC
Jarcho[1]	1949	173	1.73%
MacVine[5]	1949	107	5.6%
Thornton[4]	1947	67	5.9%
Nucci[2]	1946	150	6.6%
Farell[3]	1943	75	3.33%*
Miller[6]	1940	137	3.6%
Jones[7]	1933	89	3.3%
Cleveland City Hospital	1952	70	14.3%†

*2 of 66 patients; 9 were rendered sterile.
†7 of 49 patients; 14 were rendered sterile.

The material for this study consists of the patients operated upon for ectopic pregnancy on the Obstetrical and Gynecological Service at Cleveland City Hospital between July 1, 1948, and March 31, 1952. There were 63 such patients. These patients were all clinic patients operated upon and cared for by the Resident Staff of this hospital under the supervision of the Visiting Staff.

Of the above-mentioned 63 patients there were 26 patients who were not candidates for salpingography. Ten of these patients had had bilateral salpingectomies on the first laparotomy, 7 had repeat ectopic tubal pregnancies, and the remainder were subjected to subsequent tubal ligation or hysterectomy for varying indications. The total number studied by salpingography was 25. We were fortunate enough to secure salpingograms on two patients between their original ectopic and their repeat ectopic pregnancies. These will be discussed later.

The patients studied reported to our Outpatient Clinic for follow-up examination and their inpatient and outpatient records were reviewed with special reference to pregnancies prior to and subsequent to surgery. Specific and detailed check was made for a history of pelvic inflammatory disease prior to surgery. The patients were then scheduled for hysterosalpingography following their next menstrual period.

The radiopaque substance used in this study was Iodochloral.* After a vault preparation, the patient was draped, catheterized, and the uterine cavity sounded. The oil was then injected into the uterus with a flexible-tipped cannula protected with a soft rubber acorn. Injection was slow and was stopped when the patient complained of pain. At this point a roentgenogram was taken. If the tubes were well outlined at this point, no further oil was injected. If the tubes were not outlined, injection was continued slowly and further x-rays were taken. Over 6 c.c. of oil was rarely necessary to outline the tubes. A 24 hour follow-up film was taken the next day to determine intraperitoneal "spill," if any occurred. The salpingograms were done on a cystoscopic table equipped for x-ray. A Potter-Bucky diaphragm was used with soft tissue x-ray technique. The 24 hour film consisted of a standard anterior-posterior flat plate taken in the upright position. Premedication given was atropine, $\frac{1}{150}$ grain, and in very apprehensive patients, Demerol, 75 mg.

*Iodochloral, Searle.

X-ray films were read by representatives of the X-ray Department and the authors as representatives of the Obstetrical and Gynecological Department independently of one another. On most points concerning interpretation we were in accord. Where this was not the case, the films were discussed by members of both departments and repeat films taken if necessary to reach a decision on definitive pathology. The chief doubt in our minds that had to be resolved concerned the amount of distal tubal dilatation which represented actual hydrosalpinx as opposed to the amount which represented normal variation in tubal caliber. Of course, the latter can be accentuated by the pressure of the oil when the distal end of the tube is partially blocked. These questions of the degree of lesser pathology were, as always, the most difficult in the interpretation of films of this type, and a sincere attempt was made not to "over read" the pathology present.

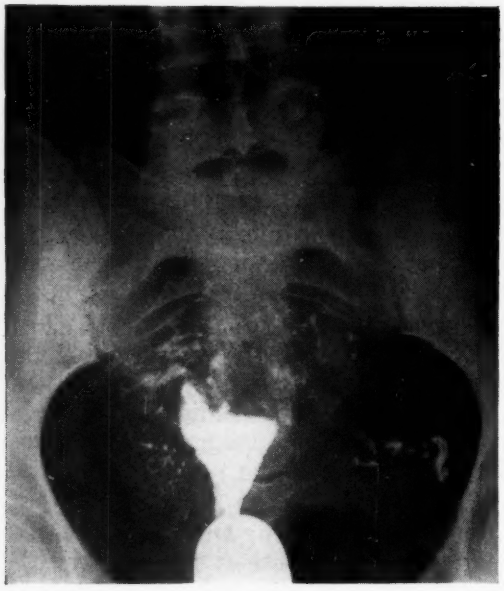

Fig. 1.—(No. 183937) Perforation of right cornu. The residual tube shows the kinking and tortuosity typical of peritubal adhesions.

Although the cornua and residual tube were the focus of our greatest interest, notations of pathology of the cervix, uterus, and adnexa were made and reported in table form. On the previously resected side we looked for cornual sphincter spasm, segments of tube which were left behind, and possible recanalization. The residual tube was studied for abnormalities in length, position, tortuosity, and patency. Displacement of the tube by extrinsic masses was nicely demonstrated in one case. The 24 hour film was used to demonstrate delayed intraperitoneal "spill," if any, "pooling" or "puddling" intraperitoneally, and the coalescence of oil in the dilated distal end of a dependent hydrosalpinx.

All salpingograms were done as an outpatient procedure with the patients spending about an hour and a half under observation following the procedure. The only ill effects noted were cramping lower abdominal pains experienced in widely varying degrees by different patients during the injection of the oil. There were no delayed ill effects noted. In one case the cannula was inserted inaccurately and the right cornu (previously resected) was perforated. The

film showed a heavy intraperitoneal "spill" of oil from the site of perforation (Fig. 1). This patient was carefully observed and suffered no ill effects, in fact, carried an intrauterine pregnancy to a term, normal vaginal delivery within 14 months of perforation. Recheck salpingograms taken 18 months after the accidental perforation revealed no defect of the involved cornu and the residual patent tube showed only slight kinking. One case showed moderate intravasation of the radiopaque oil into the veins of the broad ligament. Outside of frightening the operators, this case had no sequelae (Fig. 2).

Although fully one-half of the cases studied showed evidence of chronic pelvic inflammatory disease, none of them had any acute episodes following salpingography. Care was taken, of course, not to do the procedure on any patient with recent exacerbation of the disease. With this precaution, we believe that salpingography is not dangerous to these patients. There were no deaths in the series of 70 consecutive operations for ectopic pregnancy.

Fig. 2.—(No. 203698) Severe lower segment spasm with intravasation on the right. Twenty-four hour film showed definite coalescence in small dependent hydrosalpinx.

Results

For purposes of analysis, the cases were divided into two groups according to whether the tubes were patent or occluded. The frequency of various diagnoses in these two groups is shown in Table III. There were a total of 16 cases showing patency of the residual tube and 9 cases showing occlusion.

Occluded Group.—

In the occluded group the two major causes of occlusion were cornual spasm and tubal disease which had progressed to severe hydrosalpinx. We have included in this second group all cases of occlusion as diagnosed by salpingogram. The 4 cases attributed to cornual spasm were checked by uterotubal insufflation with carbon dioxide. Three were negative at pressures to 200 mm. of mercury. The remaining one was positive at 180 mm. of mercury. We were unable to follow the last-mentioned patient until we saw her with her second ectopic tubal pregnancy 24 months after the first ectopic and 19 months after her tubal studies.

There was one case in the occluded group which showed a large retort-shaped residual tube and no media in the peritoneal cavity on the 24 hour film. A positive gas insufflation test had been previously reported at 180 mm. of

TABLE III. FINDINGS BY HYSTEROSALPINGOGRAPHY IN 16 PATIENTS WITH PATENT AND 9 WITH OCCLUDED TUBES

DIAGNOSES	PATENT GROUP—16	OCCLUDED GROUP—9
Normal residual tube	4	0
Perisalpingitis	9	3
Mild	1	0
Moderate	4	0
Severe	4	3
Hydrosalpinx	7	3
Mild	4	0
Moderate	1	0
Severe	2	3
Extratubal pooling	4	0
Ovarian cyst (Fig. 3)	1	0
Lower segment spasm	2	0
Cornual spasm	0	4
Intravasation	2	0
Cervicitis	4	2
Congenital abnormalities	2	0
Deviation of uterus from normal position	5	2

mercury. Because of the clear-cut pathology on salpingogram we interpreted this to be a "false positive" due to gas filling the large hydrosalpinx (Fig. 4).

There were 3 cases in the occluded group in which the obstruction was at the fimbriated end of the tube with frank hydrosalpinx. There was only one case in which there was obstruction noted in the isthmic portion of the tube. The obstruction was approximately 1 cm. distal to the cornu and the uterus was noted to be bound down by multiple adhesions and rotated to the right and posteriorly. There was no history of pelvic inflammatory disease before or after surgery and none noted at surgery. We have inferred, therefore, that this is one case in which the pathology can be attribued to blood in the peritoneal cavity and its subsequent organization.

There was a definite history of pelvic inflammatory disease and sterility of from five to ten years elicited in 5 of the 9 patients in this group. In all of these 5 cases, pelvic findings at the time of surgery bore out the history. We were able to demonstrate tubal pathology (marked perisalpingitis and hydrosalpinx) in 4 of these 5 cases. Cornual spasm prevented outlining the tube in the other case. There was only one pregnancy following the ectopic pregnancy in this group and this was the repeat ectopic pregnancy mentioned previously. Average follow-up of these patients was two and one-tenth years.

The average time which elapsed between admission to the hospital and surgery in the occluded group was nine and six-tenths hours. Attempts to correlate the severity of disease in the residual tube with the length of this interval and the amount of blood in the peritoneal cavity and its degree of organization failed. There was no history of previous abdominal surgery or tuberculosis noted. The only consistent finding was a history and the physical findings of pelvic inflammatory disease.

Patent Group.—

In this group of 16 patients there were 4 with perfectly normal residual tubes. There was no history of previous pelvic infection in these 4 patients

and 3 of them had had previous children normally. One patient had a history of 2 cesarean sections, four years and two years, respectively, prior to her tubal pregnancy. At laparotomy for her ectopic tubal pregnancy the residual tube was deemed normal and the pelvis free from adhesions. Salpingograms confirmed this.

Fig. 3.—(No. 186900) Outlining of right ovarian cyst.

Fig. 4.—(No. 198637) A 24-hour film on the case demonstrating a "false positive" gas insufflation test. The coalescence of the opaque medium into droplets is typical in a dependent hydrosalpinx.

Perisalpingitis with kinking of the tube due to adhesions was the most common diagnosis in the remaining 12 cases of this group. This was diagnosed in 9 cases. There were 7 cases of hydrosalpinx, albeit only 2 of them severe, which fell into this group. The fact that a hydrosalpinx could be patent surprised us and these cases were further investigated with uterotubal insufflation with carbon dioxide. In all of the cases the patency was confirmed. Review of the salpingograms and the 24 hour films failed to indict possible recanalization on the resected side and substantiated patency of the diseased tube. It is entirely possible that the hydrosalpinx outlined on the films, especially that of lesser degrees, is an artifact caused by narrowing of the opening at the fimbriated end. Since this too represents pathology we have kept the cases in the hydrosalpinx classification.

Of those patients with diseased but patent tubes, only 3 had a definite history of pelvic inflammatory disease. Two more had a history of sterility of from five to ten years' duration but no symptoms. Two patients had had abdominal surgery five years prior to their ectopic pregnancies. There are, therefore, 7 patients in all this group with histories suggestive of tubal pathology. Those with a definite history of pelvic infection (3) were shown on surgery to have severe pelvic and peritubal adhesions. Two of the 3 had definite clubbing. Those patients with sterility and those with previous abdominal operations showed minimal or no pelvic adhesions at surgery. There was one patient who showed severe adhesions and tubal disease on laparotomy who had no history or suggestive symptoms.

Thus, there were 8 patients with little or no demonstrable pelvic pathology at surgery besides their ectopic pregnancy who were shown to have demonstrable tubal defects on salpingography. Interrogation of patients concerning irregular bleeding, pain, vaginal discharge, and other symptoms in the interval between the operation and our studies failed to produce definite evidence of new pelvic infection.

Correlation of tubal disease on salpingography with the amount of blood in the peritoneal cavity, its organization, and elapsed time between admission and surgery was more revealing here than in the occluded group.

The paucity of cases listed in Table IV of course makes the drawing of conclusions based on statistics impossible. We did feel, however, that this table shows the advantage of surgery as early as possible in ectopic tubal pregnancy. As is the routine in our hospital, as complete a peritoneal toilet as possible was effected on all of the patients operated upon. We also inferred from these figures that the patient with sudden, acute ruptured tubal pregnancy with severe intraperitoneal hemorrhage stands less chance of residual tube damage, this, as is probably generally presumed, being due to evacuation of the intraperitoneal blood before the organization of that blood has progressed sufficiently to form peritubal adhesions.

TABLE IV. CORRELATION OF TUBAL ABNORMALITIES AS NOTED BY HYSTEROSALPINGOGRAPHY WITH CONDITIONS NOTED AT OPERATION

	INTERVAL BETWEEN ADMISSION AND SURGERY		INTRAPERITONEAL BLOOD		
	MORE THAN 12 HOURS	LESS THAN 12 HOURS	MORE THAN 250 C.C.	LESS THAN 250 C.C.	ORGANIZED CLOTS
Tube normal at surgery and on salpingography (4 cases)	1	3	3	1	0
Tube normal at surgery and diseased on salpingography (8 cases)	6	2	3	5	4

In the reading of the films in this study, particular attention was paid to the stump of the residual tube, or, if cornual excision was done, to that cornu resected. The operative notes in 17 cases stated that cornual excision was done

on the affected side. In 11 of these cases the small beadlike formation at the internal os of the tube which indicates tubal "sphincter spasm" was present. Distal to this sphincter, in 10 cases, residual tube was noted in lengths varying from 3 to 10 mm. In the remaining cases where simple amputation of the tube was performed there were 2 cases in which 1 and 6 cm., respectively, of tube were left in. It would seem that the more tube left behind, the greater the chances of recanalization. There were, however, no cases where the resected side recanalized.

Follow-up of the patients in regard to pregnancies which occurred after the ectopic pregnancies showed that in the occluded group there was only one who conceived and this was the repeat ectopic pregnancy already mentioned. The patent group had 4 pregnancies. There were 2 which reached term at 24 and 36 months following the ectopic pregnancies; one early abortion 26 months following the ectopic; and one repeat ectopic 24 months after the original ectopic and 14 months after salpingograms.

We were fortunate enough to obtain salpingograms on 2 patients between their ectopic pregnancies. These were of some interest and their case histories are briefly reviewed here.

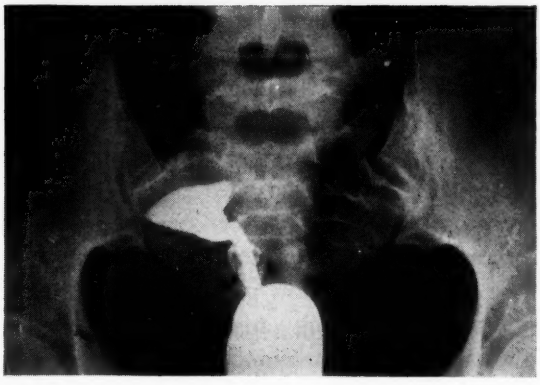

Fig. 5.—(No. 196059) "Dog-eared" configuration of the left cornu typical of cornual spasm. This case had a positive gas insufflation test at 180 mm. Hg, and was one of the 2 cases of repeat tubal pregnancy reported (Case 6).

CASE 1.—A 23-year-old Negro woman with a 5 year history of sterility and treatment for pelvic inflammatory disease in our clinic was admitted May 17, 1949, with a ruptured right ampullary tubal ectopic pregnancy. She was operated upon five hours after admission and the right tube was resected. The remaining tube was described as being bound down and clubbed and many peritubal adhesions were present on both sides. Her recovery was uneventful.

Three months and 15 months after her ectopic pregnancy salpingograms were done. Both sets of films showed patency of the residual tube, mild dilatation of the distal one-third of the tube (not diagnostic of hydrosalpinx), and moderate perisalpingitis. Chronic endocervicitis was diagnosed on the first set of films. The Rubin test was positive at 180 mm. of mercury.

Twelve months later the patient was admitted for removal of a left adenexa mass. This proved to be a large simple cyst of the ovary. Due to dense adhesions the left tube was sacrificed with the specimen. On microscopic section of this tube there was definite evidence of an early tubal pregnancy.

CASE 6.—This is the case of a 26-year-old Negro woman with a 10 year history of sterility and a 6 year history of treatment for pelvic inflammatory disease in our clinic. She was admitted in July of 1949, with an acute ruptured right tubal pregnancy. The pelvis showed evidence of mild pelvic inflammatory disease and the resected tube was reported as being the site of salpingitis isthmica nodosa as well as of the tubal pregnancy.

Salpingograms did not show the residual tube due to severe cornual spasm. A Rubin test was positive at 180 mm. of mercury. Unavailability of the patient made further studies impossible.

Two years after her first ectopic pregnancy the patient was admitted and operated upon for a ruptured left tubal pregnancy. Convalescence following both admissions was uneventful (Fig. 5).

Fig. 6.—(No. 210921) Bicornuate uterus with partially amputated horn and perisalpingitis of the residual tube.

In Case 1 we have described a case with proved patency and demonstrable perisalpingitis. This would be the type of case in which one would expect a repeat ectopic pregnancy. We have, however, in the "patent but diseased group," many solitary tubes which show much more kinking and tortuosity, and, outside of the ectopic, there has been only one pregnancy and that one terminated in an early abortion. The question then arises, Will others in this group repeat their ectopic pregnancies? Certainly their chances seem better than average but careful follow-up for many years will be necessary to substantiate this fact.

In Rubin's[8] studies by uterotubal insufflation on a group of patients who had previous ectopic pregnancies, he states that with pressure of 150 mm. of mercury or more, "though some degree of patency was present, the succeeding pregnancy was apt to be another ectopic." This is borne out in Case 1.

Case 6 brings up another question as to what part, if any, cornual spasm plays in the etiology of ectopic tubal pregnancy. Four out of 8 of the occluded cases showed cornual spasm and 1 of the 4 showed severe lower uterine segment spasm associated with the cornual spasm. In the case reviewed there was definite evidence of perisalpingitis when the laparotomy was done for the first ectopic pregnancy. If we could have got the dye into the tube, there probably would have been visible pathology. In the other 3 cases of cornual spasm no peritubal adhesions were noted at surgery and the Rubin test was negative in all cases.

This indicated to us that the same hyperirritability which existed during the first study existed during the second. Does it exist in the presence of the motile sperm or the fertilized egg, thus impeding their travel? Probably not, because the 3 patients without apparent tubal disease in the residual tube at surgery had all carried two or more babies to term before the ectopic pregnancy. The remaining patient had other pathology which could account for her ectopic pregnancy. It is interesting to note that the cornual spasm was present to a much more severe degree on the side of the solitary tube in all cases.

Table III lists 2 cases of congenital anomalies. One of these was an obvious bicornuate uterus. The other showed a configuration suggestive of a uterus arcuatus but might well represent an artifact resulting from severe combined lower segment and bilateral cornual spasm. The bicornuate uterus film also showed rather severe residual tube damage (Figs. 6 and 7).

Fig. 7.—(No. 148104) Configuration suggestive of uterus arcuatus. The solitary tube shows kinking and is patent.

Comment

We were unable in this series to indict remote surgery, genital tuberculosis, or the hematosalpinx which is occasionally present in the uninvolved tube as causes of postectopic tubal damage. The offenders were pelvic inflammatory disease and the ectopic pregnancy itself. In a total of 9 cases (5 of the occluded group and 4 of the patent group) pelvic inflammatory disease was present. As previously mentioned there were 8 cases in which the ectopic surgery itself was the evident cause of postoperative tubal abnormalities.

The incidence of pelvic inflammatory disease preceding ectopic pregnancy as reported in large series of cases varies from 13.4 per cent[4] to 52.8 per cent.[1] This wide variation is undoubtedly due to the variation in the types of patient groups studied. Our own 36 per cent incidence is to be expected with the group with which we deal and probably accounts for our incidence of ectopic pregnancy as well as the high recurrence rate.

The most distressing fact brought to light, however, is the high incidence of damaged residual tubes, whatever the cause. Most authors writing on the subject of ectopic pregnancy stress the value of conservative operative pro-

cedure, supportive measures, and speed of both diagnosis and surgery. Many of these patients have a long history of sterility and it is indeed difficult for the surgeon to bring himself to remove both tubes in some cases. But surely in the presence of a damaged residual tube sterility seems better than the increased risk of a repeated ectopic pregnancy. The breaking up of peritubal adhesions and tubal plastic procedures on the solitary tube seem to us to be of doubtful value when undertaken at the time of laparotomy for tubal pregnancy. When the residual tube is clubbed and obviously of no further service to the patient the simple cornual resection as recommended by Falk[9] might be in order, especially if the patient's condition demands the least possible surgery.

The advisability of employing hysterosalpingography as part of the routine follow-up of all patients operated upon for ectopic tubal pregnancy is established in our minds. Not only is it helpful in advising the patient of her prognosis for future pregnancies but it also gives the operator an unexcelled opportunity to study by hysterosalpingography the pelvis he has already examined at surgery. Also, of course, additional cases studied, as well as long-term follow-up of those reported here, may strengthen or detract from conclusions drawn from our small series.

Summary

1. A series of 70 consecutive patients operated upon for ectopic pregnancy is reviewed briefly. An unusually high recurrence rate (14.3 per cent) is noted at Cleveland City Hospital.

2. Twenty-five of these cases were studied by hysterosalpingography following the operation for ectopic pregnancy. Sixteen patients showed patent residual tubes, 9 showed occlusion. Only 4 showed a normal residual tube. The various diagnoses are shown in chart form and are discussed.

3. Two cases of repeat ectopic pregnancy which were studied between operations are presented and discussed.

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SICKLE-CELL ANEMIA COMPLICATING PREGNANCY

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WITHIN the past few years, the significance of sickle-cell anemia complicating pregnancy has become more evident. It is hard to say whether the increased frequency with which the diagnosis is made is due to the more detailed blood studies now commonly conducted or to an increasing familiarity with the symptoms and complaints of these patients.

Sickle-cell anemia is a hereditary type of chronic hemolytic anemia, peculiar to Negroes or persons with an admixture of Negro blood. This condition, transmitted as a Mendelian trait, may be characterized clinically by anemia, jaundice, rheumatoid manifestations, fever, nausea and vomiting, recurrent attacks of abdominal pain, leg ulcers, and signs of cerebral irritation. It is distinguished by the presence of peculiar sickle- and oat-shaped cells in the peripheral blood, as well as by signs of excessive blood destruction and active blood regeneration. From time to time the clinical manifestations appear abruptly, these episodes being designated as crises.

Sickle-cell anemia must be distinguished from sicklemia or sickle-cell trait, in which there is a tendency for only a small percentage of red cells to sickle and in which there is no evidence of active blood destruction and regeneration. The relationship of the two conditions is not entirely clear. Some individuals with the sickle-cell trait are known to go through life without ever showing the anemia. When the active form develops, it usually begins in the first two decades of life, and once the active process is initiated, it does not disappear. Diggs, Ahman, and Bibb[1] found that the incidence of sickle-cell trait in Negroes was 7.3 per cent and that one in 40 in this group had sickle-cell anemia. Beacham and Beacham[2] report an incidence of 8.3 per cent of sickle-cell disease from the Charity Hospital in New Orleans, while Fouché and Switzer[3] give an incidence of 14.2 per cent among the Negro population of South Carolina.

From April, 1948, through September, 1952, there were 7,784 deliveries on the Obstetrical Service of the Morrisania City Hospital. During this period there were 9 cases of sickle-cell anemia with hemolytic crises occurring during pregnancy. Thus the incidence was 1 in 865 deliveries.

The paucity of reported cases of sickle-cell anemia associated with pregnancy is understandable since most patients die early in life, and there is the possibility of infertility with this blood dyscrasia. Only about 75 cases of this disease associated with pregnancy have been reported in the literature, and most of these have been during the last few years. The maternal mortality rate is given as approximately 23 per cent and the fetal loss has been reported to be over 30 per cent.

The 3 cases of sickle-cell anemia which occurred during the first eighteen months of this report were treated empirically with antibiotics, chemotherapy, and transfusions of whole blood. In these three cases, all the babies and one mother were lost. In the three succeeding cases there were no fetal or maternal deaths. The last group of three cases occurred in the past year and resulted in one live birth, one full-term stillbirth, and an abortion at 20 weeks of gestation.

The age incidence of the patient in this series ranged from 19 to 33 years. All were primigravidas except two. One patient, attended during her fourth, fifth, and sixth pregnancies, was the oldest patient in this series.

While several cases have been described in white persons, it is generally conceded that there must be some mixture of Negro blood, since sickle-cell anemia is essentially peculiar to the Negro race. One apparently white female patient with sickle-cell crises in pregnancy was found in this group of 9 cases, but closer investigation into the patient's past history revealed that her father was of Ethiopian extraction and his mother Eritrean.

The past histories of all these patients followed a similar pattern. In each, sickle-cell disease was discovered before puberty because of attacks of chest pain, cough, breathlessness, lassitude, increasing fatigue, rheumatic pains, migratory joint pains, marked anemia, and abdominal pains with or without subsequent appendectomy.

The usual blood picture was one of a normocytic, normochromic type of anemia with a red blood count that varies between 2.0 and 3.5 million. When the anemia in this disease becomes severe, however, there is a tendency toward macrocytosis. On stained smears, the great majority of red cells are usually round or oval with anisocytosis, poikilocytosis, and anisochromia. Nucleated red cells are usually present and especially so following or during a crisis. The white blood counts in this series ranged from 10,000 to 31,000 with a polymorphonuclear shift to the left. The platelet, bleeding, and coagulation times were always within normal limits. The reticulocyte count varied with the degree of activity; the more acute the process, the higher the count and with recovery the return of the reticulocyte count to normal. All patients showed an increase in the icteric index with figures reaching as high as 55, and urobilinogen was found in dilutions ranging from 1:40 to 1:160. One hundred per cent sickling after twenty-four hours was noted in all the cases.

Physical examinations of these patients varied with the degree of erythrocyte destruction and the severity of symptoms. Dyspnea, palpitation, pain, drowsiness, fatigue, pallor, jaundice, fever, tachycardia, cardiac enlargement, abdominal tenderness, cough, variations in breath sounds, and leg and joint pains have been most frequently encountered in this series.

After a review of the results in the first three cases, it was evident that our treatment of the patient with sickle-cell anemia was not entirely satisfactory. Whereas the value of blood transfusions during a crisis was thought to be debatable, since transfusions may suppress the bone marrow, we have come to believe that blood is the essential factor in successful treatment.

Despite the fact that these patients develop reactions, it is our present belief that failure to give sufficient blood to overcome the anoxemia in the infant resulted in fetal death.

TABLE I. CLINICAL CHARACTERISTICS IN CASES OF THIS SERIES

CASE NO.	PRESENT AGE	AGE OF ONSET	COMPLAINTS AT ONSET OF DISEASE	PARITY
1	19	6	Cough, chest pain, breathlessness	0
2	22	9	Lassitude, cough, increasing fatigue, appendectomy, for abdominal pain	0
3*	31	Childhood	Fatigue, increasing breathlessness, generalized swelling	4
4*	32	Childhood	Fatigue, increasing breathlessness, generalized swelling	5
5	22	11	Migratory joint pains	0
6	19	12	Marked anemia, signs and symptoms of rheumatic fever	0
7	23	Childhood	Marked anemia	1
8	24	6	Possible rheumatic fever	0
9*	33	Childhood	Fatigue, increasing breathlessness, generalized swelling	6

*Same patient in successive pregnancies.

The hematocrit determination is the basis on which we judge the patient's need for further transfusions. We try to maintain the hematocrit between 25 and 30, for below this level signs and symptoms of anemia with the ensuing anoxemia develop. During a crisis, the reticulocyte count is high, but as the crisis subsides, the count approaches normal.

Sickle cells are known to be poor oxygen carriers. It is important, therefore, to overcome the anoxemia that develops in the fetus. For this reason we have given oxygen by mask to patients in crisis, during labor, and delivery. This anoxemia was demonstrated in the loss of the baby in the second, third, and seventh cases, but was apparently compensated for in the fourth, fifth, sixth, and eighth cases when the transfusions were given and oxygen was administered.

Since these women are prone to infections, the incidence being in direct proportion to the degree of anemia, antibiotics and chemotherapy have been employed. In order to maintain good nutrition, high-carbohydrate and high-protein diets have been supplemented by vitamin therapy. We have found, however, that iron therapy alone has no value.

TABLE II. SPECIAL THERAPEUTIC MEASURES AND RESULTS IN NINE CASES OF SICKLE-CELL ANEMIA

CASE NO.	BLOOD TRANSFUSED	OXYGEN	MEDICATIONS	INFANT	MOTHER	REMARKS
1	500 c.c.	None	Penicillin sulfadiazine	Neonatal death	Died	None
2	2,200 c.c.	None	None	Stillbirth	Recovered	None
3	2,000 c.c.	None	None	Stillbirth	Recovered	None
4	900 c.c.	Yes	Penicillin	Live birth	Recovered	None
5	4,850 c.c.	Yes	Penicillin	Live birth	Recovered	None
6	4,000 c.c.	Yes	Penicillin	Live birth	Recovered	None
7	3,500 c.c.	None	None	Stillbirth	Recovered	Refused hospital
8	4,500 c.c.	Yes	Penicillin	Live birth	Recovered	None
9	1,000 c.c.	Yes	Penicillin	Abortion	Recovered	Refused hospital

It is our belief that if the baby is viable at or near term, and the mother's condition is good, the induction of labor may possibly save a baby that otherwise might be lost by the unpredictable occurrence of a crisis. If there are no contraindications to vaginal delivery, rupture of the membranes with medical induction has been our method of choice. We are now using intravenous Pitocin as our inducing agent. If an obstetrical indication for cesarean section exists, then it should be performed at the proper time.

Case 5 will be briefly described to illustrate a typical case of sickle-cell anemia occurring during pregnancy.

A 22-year-old Negro primigravida, due to deliver in October, 1950, was admitted on July 29, 1950, and again on Aug. 12, 1950, in crisis. At 11 years of age when she was hospitalized for migratory joint pains, the diagnosis of sickle-cell anemia had been made. Of 8 siblings, 2 children had died of sickle-cell anemia. The two crises which occurred during pregnancy were treated with supportive therapy, antibiotics, and transfusions of 2,350 c.c. of whole blood. After the crisis had passed, the patient signed herself out of the hospital against our recommendation. On September 4, she returned with complaints of muscle aches and joint pains. Even though active sickling was not demonstrated, she received 1,000 c.c. of blood because of a marked anemia. On October 3, she had another crisis and received 1,500 c.c. of blood and oxygen therapy. On Oct. 11, 1950, one week from term, labor was induced with intravenous Pitocin after artificial rupture of the membranes. After 12 hours of labor, she was delivered spontaneously of a living 5 pound male infant. Oxygen therapy was given during labor. On the first day post partum, she received a transfusion of 500 c.c. of whole blood, and was given supportive therapy and penicillin prophylactically. Mother and baby were discharged in good condition. Sickle-cell preparations on the infant's blood were negative, which is not very significant since it usually takes 4 months before the fetal hemoglobin disappears and a positive sickling reaction is possible.

Summary

1. Nine cases of sickle-cell anemia complicating pregnancy have been reported.

2. On an obstetrical service that has a high percentage of Negro patients, sickle-cell anemia should be ruled out when a patient manifests signs of anemia, abdominal or joint pains.

3. Transfusions of large quantities of whole blood are given to these patients to maintain a hematocrit between 25 and 30. These transfusions are given whether a crisis exists or not.

4. Oxygen administered to a mother during crisis, labor, and delivery seems to protect against anoxemia in the baby.

5. Antibiotics and chemotherapy have been used prophylactically to combat infection. High-vitamin, high-carbohydrate and high-protein diets have been given to maintain good health in the mother.

6. It is our belief that, before further crises develop and prove fatal to the baby, termination of the pregnancy should be effected at or near term when the baby is viable and the mother in good condition.

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THE DEVELOPMENT OF TOTAL BLINDNESS AS A COMPLICATION OF PREGNANCY

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TOTAL blindness as a complication of pregnancy is such a rare entity that, having observed such a case, we were prompted to report it. The following is a presentation of a case and a review of the world literature on this subject.

Case History

The patient, a 22-year-old primiparous Negro woman, was admitted July 21, 1952, to Queens General Hospital at term in early labor. Her last normal menstrual period was Oct. 13, 1951, and her expected date of confinement, July 21, 1952. The prenatal course, except for a 30 pound weight gain and ankle edema for one month, was relatively uneventful.

The patient had venereal disease at the age of 17 (the nature of which was unknown to her). She received four days' treatment and was discharged as "cured." Her VDRL and blood Wassermann tests were negative during this pregnancy. She had no other known diseases and denied having had any surgery.

A physical examination revealed a well-developed, well-nourished woman in early labor. Her blood pressure at this time was 140/80, pulse 80, temperature 98.6° F., and respirations 16. An abdominal examination demonstrated a gravid uterus at term. By x-ray pelvimetry an ample gynecoid-type pelvis was reported. Laboratory reports included: hemoglobin 10.5 Gm., white blood count 15,600, red blood count 3.5 million, urine negative for albumin and acetone.

On July 22, after 22 hours of labor and 3 hours of ruptured membranes, the vertex presented at zero station as a left occiput transverse. Attempts at manual rotation and rotation with Kielland forceps were unsuccessful and the patient was taken to the operating room. At this time her blood pressure was 150/90, pulse 100, and the fetal heart was heard in the left lower quadrant at the rate of 150 per minute.

At 2:15 P.M., a Norton type paravesical extraperitoneal cesarean section was performed with minimal difficulty, and a 7 pound nonmacerated stillborn infant was delivered. The fetal heartbeat was heard just prior to surgery. Anesthesia was by open drop ether; attempted spinal anesthesia was unsuccessful. Blood loss was estimated at 500 c.c. During the operative procedure, the patient's blood pressure was 200 mm. systolic for a short period of time.

At 4:00 P.M., the patient was returned to the obstetrical floor. At this time, the blood pressure was 80/50. Vasopressors and whole blood returned the blood pressure to 150/100. Urinary albumin was reported as 1 plus.

On July 22, 14 hours after the operation, the patient complained of being unable to appreciate light. An emergency eye consultation was secured and the report was as follows:

Lids and adnexa normal, pupils in mid-dilatation and fixed, media clear, both retinas edematous, no hemorrhages in the right eye, the left eye shows one flame hemorrhage temporal to disk. Right disk well outlined, left blurred, veins normal, arterioles constricted. Diagnosis: Embarrassment of retinal arterial circulation, not determined whether on basis of spasm or closure.

The patient was placed on intravenous papaverine, anticoagulants, and a stellate ganglion block was performed on the left side, the side most involved. She continued to be unable to see or appreciate light. An electroencephalogram demonstrated diffuse delta activity.

Other pertinent data at this time were as follows: skull plate of sella turcica normal; prothrombin 100 per cent activity; total proteins 7.5 Gm.; albumin 3.8 Gm.; globulin 3.7 Gm.; carbon dioxide combining power 43 per cent; blood type 0, Rh positive; Wassermann test negative; hemoglobin 10.5 Gm.; red blood count 3.7 million; white blood count 15,600; negative for sickling; urea nitrogen, 15.0.

On the second postoperative day, the patient continued to be unable to perceive light. Both disks were now obliterated with pallor of retinas and papilledema. Cerebral angiograms were reported as normal.

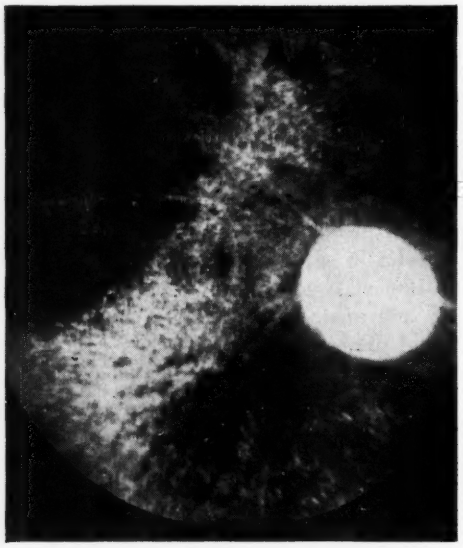

Fig. 1.—Funduscopic photograph of right eye, taken September 23, demonstrating optic atrophy, retinal degeneration, and pigmentary disturbances. The shrunken arteries are visible as thin white lines.

On September 23, two months postoperatively, both pupils were widely dilated and did not react to light. There was no light perception in either eye. Media, muscles, and tension were normal. The fundus of the right eye disclosed a closure of the central retinal artery with much generalized retinal degeneration. There was evidence of perivascular sheathing as is observed after papilledema. There was also marked retinal degeneration with pigmentary disturbance and an overgrowth of glial tissue. The disks, which revealed atrophy, were white and sharply outlined. The arteries were shrunken and were represented by white lines (Fig. 1).

The case presented in this report fits the descriptive picture of central retinal artery thrombosis as outlined in May's text.[1] There were no external eye signs other than mydriasis, but the ophthalmoscopic picture was very characteristic; the fundus became pale and edematous. The characteristic cherry-red spot of the fovea was not present due to the severe retinal ischemia. The arteries were thin and faded as the periphery of the fundus was approached. Degeneration of the retina occurred in a few days and the end result was atrophy of the nerve fibers and ganglion-cell layers. The end result in this condition of central retinal artery thrombosis follows this pattern:

the edema subsides; retina and disk atrophy, the latter becoming white, with sharply defined outline; the arteries become shrunken and may be represented by white lines. If there have been hemorrhages, these are replaced by areas of degeneration, sometimes marked with cholesterin or pigment deposits.

The foregoing description applies to cases in which the main trunk of the central artery is occluded, as was the situation in our case. The embolus or thrombus may, however, lodge in one of the branches of the central artery. In such cases, interference with sight and the changes in the background will be limited to the area supplied by the occluded branches. Central vision will be preserved, but there will be a sector-shaped defect in the field. The blindness may be preceded by a short prodromal attack of blurred vision, probably due to a spasm of the central retinal artery. Perera[1] states that a thrombus causing an occlusion is more common than an embolus and that it usually follows an endarteritis in arteriosclerosis. When an embolus is the cause, it is usually dependent upon mitral stenosis which has been the seat of a fresh endocarditis; less often the embolus is the result of atheroma, aneurysm of the aorta or carotid artery, nephritis, and pregnancy. In rare instances, in which the patient has recovered good vision, the blocking has probably resulted from a temporary spasm of the walls of the artery. Suggested treatment includes: early paracentesis of the cornea, inhalation of amyl nitrate, nitrites given intravenously, acetylcholine given subcutaneously or subconjunctivally, and massage of the eyeball to drive the plug into smaller branches where it will be less serious. Good results have been reported in some cases, but generally the prognosis is poor.

Review of the Literature

Eastman[2] reports that in 1 to 2 per cent of cases of eclampsia, blindness occurs. It may be as a result of the edema of the retina, in which case it usually disappears spontaneously, or it may be central in origin, caused by some disturbance in the optic nerve or in the visual center in the occipital lobe. He further states that the blindness may persist for a few hours or for several weeks. Usually, however, the vision returns to normal within a week and the prognosis for sight is good. Occasionally, hemorrhagic retinitis or detachment of the retina is observed. Eastman reports 132 cases of eclampsia in which Schiotz, by ophthalmologic examination, found 7 cases of retinal detachment with 2 persisting for years. In conclusion, he states that the prognosis of ocular lesions accompanying eclampsia is surprisingly good and most cases of incomplete and complete detachment of the retina result in no permanent impairment of vision.

Dieckmann[3] states that scotomas, diplopia, and dimness of vision are not indicative of toxemia in normal pregnancy, but are regarded as prodromal symptoms of eclampsia in patients with pre-eclampsia, with an incidence as high as 30 to 50 per cent in eclamptic patients. Blindness may be caused by edema, disturbance of the optic nerve or of the visual centers in the occipital lobe, the latter being most usual. Dieckmann reports an incidence of blindness in eclampsia from 1 to 3 per cent, and states that it may occur with or without

convulsions or coma, but is rarely seen in nonconvulsive toxemia. The amaurotic attacks are rarely of psychogenic origin, as was originally believed. The prognosis, as reported by Dieckmann, is excellent, and Schiotz states that amaurosis is not, in itself, an indication for termination of pregnancy.

The Chicago Lying-in Hospital reports no case of blindness in an eclamptic or pre-eclamptic patient since 1941. They report 4 cases, prior to 1941, of amaurosis with complete recovery and in which subsequent examinations failed to reveal any impairment of vision.

Another possible etiological factor, not often mentioned, is thrombosis of the intracranial veins. Hyland,[4] in a report of 2 cases of intracranial venous thrombosis in the puerperium, states that thrombosis of the intracranial veins has been recognized for many years as a rare and fatal complication of the puerperium. Pathologically, it has been regarded as a primary thrombosis to distinguish it from thrombophlebitis secondary to generalized or local septic conditions. Cases with recovery have been reported. The extent and nature of the symptoms depend on the distribution of the thrombosis in the dural sinus and cortical veins, but in most cases the symptoms follow a fairly uniform pattern. The symptoms usually become manifest between the fourth and twenty-first day after a normal pregnancy and labor, although cases have been reported in which the onset was much later after delivery. The early signs commonly include headache and focal or generalized convulsions, followed by monoplegia or hemiplegia with or without aphasia and occasionally bilateral involvement of the limbs. Also associated with the above findings, papilledema may be present, and amaurosis has been described. The occurrence of papilledema depends on whether or not there is severe obstruction to the superior sagittal sinus, in which event there will also be a decided elevation in the pressure of the cerebral spinal fluid.

The etiological explanation for the occurrence of intracranial venous thrombosis is not settled, according to the experimental work of Batson, as advanced by Martin.[5] A fragment of clot may be carried to the cranial veins from the pelvic veins by way of the vertebral venous system; these veins are practically devoid of valves. The fragment then acts as a nucleus for the formation of a clot.

Kendall[6] considers the intracranial venous thrombosis as primary and a result of local vessel damage during labor, assisted by three factors in the blood of puerperal patients conducive to thrombosis: (1) increase in thrombocytes, (2) increase in plasma fibrinogen, and (3) an increased "stickiness" of the blood, attributed to the presence of large numbers of newly formed cells released from the bone marrow. The damage to the vessel wall, in his opinion, occurs as a result of increased intracranial venous pressure, which, together with stasis of the blood, takes place during labor as a result of the greatly increased intra-abdominal tension and forced expiratory efforts against a closed glottis.

As far as therapy in this condition is concerned, it is recommended that anticonvulsant medication and dehydration by the administration of hyper-

tonic fluids be given. Where occlusion of the superior sagittal sinus has occurred with an increase of cerebral spinal fluid pressure, daily removal of cerebral spinal fluid has been utilized. The use of anticoagulant therapy for the condition is recommended by some.

Givner and Jaffe,[7] in a preliminary report, call attention to the rarely occurring closure of the central retinal artery after general anesthesia. It is their belief that the combination of the following factors are needed: (1) loss of blood, or shock, (2) pressure on the eye, by an anesthesia mask, in a patient with a low nasal bridge, (3) prolonged anesthesia. Attention is called to this condition because the main treatment is its prevention.

Retinal ischemia after exsanguination is a rare event, considering the common occurrence of profound loss of blood. It usually follows bleeding from medical conditions and rarely from wounds or surgical procedures. Recurrent hemorrhages are most prone to affect the vision; the resulting blindness is usually bilateral, but is unilateral in about 15 per cent of cases, and may be transitory or permanent. It usually comes on between the third and seventh days after bleeding, but may be delayed for some time. Rarely, the picture is one of complete obstruction of the arterial circulation, occasionally even unilateral.

Sommerville-Large[8] states, in a report of a case of bilateral permanent blindness in pregnancy, "I can find no cases of permanent blindness resulting from pregnancy in the records of the Rotunda Hospital, Dublin." He therefore concludes that the case he reported appeared to be the first in over 150,000 births. The case was that of a 30-year-old woman who had a transient loss of sight in her third pregnancy, lost the sight of one eye (with marked diminution in the other) in her fourth, and went totally blind (permanently) on the fourth day after the birth of her fifth child. Six years later, she developed presenile dementia. At no time did she demonstrate albuminuria and examination of the central nervous system revealed no abnormality. There is no record of blood pressures.

The cause of blindness was attributed to "post-neuritic atrophy." By way of explanation the author concludes that occlusion of the central retinal artery (whether by spasm or embolism) produces sudden and deep blindness; and also—if the occlusion persists for a long period of time—blindness becomes permanent. These arterial blocks usually take place in the region of the cribriform plate, and may therefore be considered as too far forward in the nerve to produce papilledema. It is suggested that the papilledema which was present in the case reported could follow a severe spasm of the entire retinal artery.

Ingiulla[9] reports 4 cases of amaurosis in pregnancy. In all cases, the recovery of visual acuity was complete. He states that amaurosis during pregnancy is caused by a spasm of the retinal vessels in the majority of cases. Treatment of the spasm must be instituted early in order to prevent damage from persistent spasm. The retinal spasm may represent the local expression of a systemic hypertensive condition or the retinal ischemia may have a

central origin on the basis of edema. In Inguilla's first case, the retrobulbar injection of Novocain, nicotinic acid, and belladonna was immediately and strikingly effective. In the last two cases, the Novocain was injected intravenously to abolish vascular spasm, not only by a peripheral action, but also through an effect on the upper centers. In both cases, the intravenous injection proved effective and free of side effects. It is suggested that they be repeated once or twice daily.

Swift[10] reports a case of acute amaurosis during pregnancy without any signs of toxemia and with complete recovery of visual acuity within forty-eight hours following the emptying of the uterus. Swift concludes that the amaurosis in this case was probably due to chronic retrobulbar neuritis.

Kelly[11] reports a case of blindness discovered immediately following delivery of a 33-year-old primipara with pre-eclampsia. Examination of the urine following delivery revealed "half-solid" albumin. Recovery began immediately and visual acuity was complete in two months. A final diagnosis of uremic amblyopia was made.

Conclusions

Although blindness is a rare complication of pregnancy, every obstetrician should be alerted to the possibility of its occurrence, with or without pre-existing toxemia. In reviewing the literature, these observers were surprised by the multitude of causative factors in producing this condition. These are: (1) central retinal artery and venous thrombosis, (2) edema of the retina, (3) central disturbance of the visual center in the occipital lobe or lobes as by edema or hemorrhage, (4) detachment of the retina, partial or complete, (5) disturbance of the optic nerve, e.g., optic neuritis, (6) psychogenic disturbances, (7) intracranial venous thrombosis particularly when it involves the superior sagittal sinus, (8) retinal ischemia following recurrent severe hemorrhage, (9) persistent spasm of the retinal vessels.

Detachment of the retina, edema, and central retinal artery thrombosis are probably the most common of these factors.

Numerous therapeutic measures have been discussed with reference to the management of acute blindness when it occurs ante, intra, or post partum. These measures fall into several definite groups, based upon the etiology of the blindness. They are: (1) anticonvulsants, antispasmodics, and vasodilators; e.g., papaverine, amyl nitrite, Priscoline, Novocain, acetylcholine; (2) anticoagulants; e.g., heparin, Dicumarol; (3) decompression by paracentesis of the anterior chamber or by intravenous injection of hypertonic solutions; (4) mechanical methods; e.g., massage of the eyeball; (5) nerve blocks; e.g., stellate ganglion or retrobulbar.

Summary

1. A case study of acute blindness complicating pregnancy is discussed.
2. A review of world literature on the subject is presented.
3. Various forms of therapy are mentioned.

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ADRENAL HEMORRHAGE IN PREGNANCY

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THE death of a postpartum patient, due to adrenal hemorrhage, led us to consider the possibility of the stress syndrome as a cause of adrenal apoplexy in pregnancy. That fatal adrenal hemorrhage has been considered a rare finding is attested to by the fact that the standard textbooks either fail to mention, or scarcely describe, the condition. A thorough search of the world literature has yielded a total of only 34 cases associated with pregnancy.[1-10] That 33 of these cases were reported within the last ten years and that the majority of these reports come from the British Isles casts some doubt on the actual rarity of this condition. It is noteworthy that all of these cases, with two exceptions,[2, 7] occurred during a pathological gestation. They were all diagnosed at autopsy and in none was the true condition apparently suspected. We add a case of our own under the same circumstances.

Case Report

Mrs. M. N., a 33-year-old primigravida, was first seen in the prenatal clinic when she was three months pregnant. Past history and physical examination at that time were essentially negative. The patient's prenatal course was complicated by what appeared to be round-ligament pain on the right side, which, although discomforting, was never severe enough to require medication. The total weight gain was 19 pounds, starting at 130 pounds, and the blood pressure and urinalysis were normal throughout. The chest x-ray and blood Wassermann test were negative, she was Rh negative, with no antibodies, the white blood count was 15,700 and the hemoglobin 13.3 Gm. X-ray pelvimetric studies showed moderate midpelvic contraction.

Three weeks prior to her expected date of confinement the patient experienced a sudden episode of right lower quadrant pain associated with mild vomiting and was admitted to the hospital. Careful questioning revealed that the pain was similar to that she had been having during her pregnancy; it was, however, more severe. Physical examination revealed questionable guarding in the right lower quadrant, without rigidity or rebound tenderness. The abdomen, although enlarged with a near-term pregnancy, did not appear unduly distended, and the patient was passing flatus. The pain was most pronounced along the course of the right round ligament. The white blood count was now 17,900 with 84 per cent neutrophils Catheterized urine was negative. The temperature was 98.6° F.

The patient had been having mild labor pains prior to this episode and it was noted that the right lower quadrant pain was more severe when she had a contraction. Careful observation revealed that the pain improved on bed rest and when she was lying on the right side. The following morning the patient began to have fairly hard labor with contractions occurring at 3 to 5 minute intervals. On rectal examination the fetal head was at the spines in the transverse position; the cervix was 70 to 80 per cent effaced, but the external os was closed. The right lower quadrant pain was controlled by an ice pack and having the patient lie on her right side. Observation for the next five hours failed to reveal any progress of either cervical dilation or the presenting part, and the patient was rested with morphine and Seconal.

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During the next forty-eight hours she was given three good trials of labor, each lasting about six hours; these were, however, without benefit of Pitocin. Rectal examinations during this period revealed that the presenting part failed to descend until the last trial of labor. The cervix became effaced to 100 per cent but failed to dilate. During this period the right lower quadrant pain persisted, although it was much milder in degree. The abdomen remained soft and showed no change in size. The urine was negative and the temperature, blood pressure, pulse rate, and fetal heart tones were all normal. Hydration was maintained by daily infusions of 5 per cent glucose in saline and distilled water in addition to a limited oral intake of water and soup.

On the fourth hospital day, a sterile vaginal examination was performed which revealed the fetal head to be almost on the perineum in the transverse position. The external os of the cervix was posterior and apparently undilated for it could not be definitely located even with the use of retractors. The cervix was still completely effaced. The anterior lip was a reddish-purple color, very friable, and so thin that the sagittal suture could be palpated through it. A laparotrachelotomy was done under spinal Pentothal anesthesia on the fourth hospital day because of cervical dystocia and at this time a normal, full-term female infant was delivered without difficulty; her cry was spontaneous and her color good. Examination of the pelvis showed that the right ovary was twisted, hemorrhagic, necrotic, and very friable, measuring 8 by 3.5 by 2.5 cm. It was located just above the pelvic brim below the appendix and was removed without difficulty. The round ligament was grossly normal except for the fact that it remained tense even after the uterus was repaired.

The first postoperative day was uneventful. The second postoperative day the patient began to vomit and by the third day had developed a typical picture of paralytic ileus which was confirmed by x-ray. Wangensteen drainage and intravenous infusions of 5 per cent glucose in saline and distilled water were instituted. Although the temperature was normal, prophylactic penicillin, 50,000 units every three hours, was given. The white blood count was 19,950 with 90 per cent polymorphonuclear leukocytes. The urinary output was good.

On the fourth postoperative day the patient had a sudden episode of cyanosis and marked restlessness. The skin was cold and clammy, and the pulse was rapid, weak, and thready. Blood pressure was unobtainable. The respirations averaged 30 per minute. The cardiac rate was 150 and regular, but the sounds were weak. Chest x-ray was negative. Oxygen and 1,000 c.c. of plasma were immediately administered with improvement in the patient's condition. There was no pain other than that ascribed to the operative site. The pulse became stronger in character, but the rate remained at 100 to 120 per minute. Although the temperature was normal, streptomycin, 0.25 Gm. every six hours, was started. The patient's condition remained fair for the next 18 hours during which time she was given 4,000 c.c. of fluid intravenously and the Wangensteen drainage continued to remove large amounts of fecal-smelling, blackish-green fluid. The urinary output was low and very concentrated, with a specific gravity of 1.025 to 1.035. Clinically, at this time, there was no evidence of blood dyscrasia. At 9 P.M. the patient's pulse became unobtainable at the radial artery, and the cardiac rate was 172 per minute. The patient was restless and cyanotic with rapid, shallow respirations. Temperature was 104.5° F. rectally. An electrocardiograph revealed sinus tachycardia with no other abnormalities; the patient was prophylactically digitalized, however, in spite of the fact that there were no signs of failure. The abdomen was less distended at this time, and the patient was passing small amounts of flatus. At 4:30 A.M. the patient's cardiac rate was unobtainable although faint sounds could be heard at intervals. Respirations were rapid and shallow, averaging about 40 per minute. The blood pressure and radial pulse were unobtainable. She was very cyanotic in spite of oxygen. Temperature was 104° F., rectally. The abdomen was soft and not distended and the patient had had two bowel movements, passing soft, almost watery, greenish stools. There was no abdominal rigidity, spasm, or apparent tenderness. The patient was at this time irrational and very restless. At 5:30 A.M. she died.

A complete autopsy failed to reveal any pathological findings other than a minimal peritoneal reaction where the right ovary was excised and a healing uterine incision. The

right adrenal gland was transformed into a large sac of blood. The cortex and part of the medulla were almost completely destroyed. There were no thrombi in the adrenal veins. The intestinal tract failed to reveal any abnormalities. The pathological diagnosis was right adrenal hemorrhage, massive.

Clinical Picture

The clinical picture of adrenal hemorrhage will generally fall into one of two main groups, although variations may be noted from one case to another. The first group, into which our case falls, is characterized by a picture of acute adrenal insufficiency with superimposed pain and vomiting. There is sudden abdominal pain with tenderness over the costal margin or the lumbar or epigastric regions, generally without any associated muscular rigidity. This is accompanied by vomiting, often intractable, and some abdominal distention. The physical signs are vague and the degree of shock usually out of proportion to them. The blood pressure is low or not obtainable, the pulse rapid, weak, and thready, and the respirations rapid and shallow. There is usually an elevated temperature, which may rise terminally to 104 to 105° F. The white blood count is elevated with a marked polynucleosis. The skin is cold, clammy, and may have a dusky hue. The collapse goes on to coma and death in a variable length of time. To this picture may be added restlessness, delirium, and perhaps convulsions.

The second group is usually characterized initially by constant pain, which, often mild, becomes progressively more severe. The temperature, pulse, blood pressure, and respirations are generally normal; asthenia, however, may be prominent. There is an elevated white blood count with polynucleosis. This picture then progresses to one of collapse with all the findings of acute adrenal insufficiency. The diagnosis, if suspected, is not difficult to confirm by means of the eosinophil test,[11, 12] which will show no decrease of eosinophils on injection of ACTH. It may be made even more conclusively by a therapeutic test consisting of the intravenous administration of 50 to 100 c.c. of aqueous adrenal cortical extract. In acute insufficiency this will produce a dramatic alleviation of the symptoms.

Adrenal Physiology During Pregnancy

It is well known that the adrenal cortex undergoes hyperplasia and hypertrophy during pregnancy. Until recently, however, little work has been done to determine to what extent the cortex reacts to the increased burden imposed by pregnancy or what its place is during complicated gestations. Functional evidence of adrenal hyperactivity is seen in the relative eosinopenia found during normal pregnancy[13] with a drop of 20 per cent in the total eosinophil count early and of 30 to 40 per cent late in pregnancy.[14] This is substantiated by Venning's[15] studies of the urinary corticoids in which she noted a diphasic curve of excretion with the first peak in the first trimester and the second occurring at about the two hundredth to two hundred fortieth day of pregnancy. Other investigators have shown that the corticoid excretion during pregnancy is twice as great as during the nonpregnant state.[13, 16, 17, 18] Patients with twin pregnancies have been shown to have a higher level of corticoid excretion than those with single pregnancies.[18]

The mechanisms, hormonal or other, inducing adrenal cortical hyperactivity during pregnancy are at this time largely a matter of conjecture. Hyperplasia may result from the high levels of circulating estrogen; or the increased pituitary activity may result in increased excretion of adrenocorticotropic hormone with the same result.

The whole reaction may be explained along the lines of the general adaption syndrome, as the many changes brought about in the body secondary to pregnancy are probably nothing more than a response to the chronic stress imposed by the developing products of conception. The work of Seyle[19] has clearly demonstrated the role of the pituitary-adrenal axis in the stress or general adaption syndrome. The histological and functional alterations of adrenal cortical activity during gestation correlate well with the expected changes on the basis of this theory.

The Stress Syndrome, Adrenal Exhaustion and Apoplexy

It has been shown that once the organism has become adapted to one stress it decreases its ability to react and adapt itself to a superimposed stress. This may lead to acute adrenal insufficiency, the exhaustion reaction of Seyle, which histologically is often characterized by hemorrhage and necrosis of the adrenal cortex.

That toxemia exerts a definite stress is substantiated by the work of several investigators. Mukherjee,[20] studying carbohydrate utilization during pregnancy, demonstrated an increased function of the pituitary-adrenal axis during pre-eclampsia. Devis[17] showed that in pre-eclampsia the level of corticoid excretion is twice, and in eclampsia is seven times, that of normal pregnancy at the same time of gestation. Way,[21] on studying the autopsy reports of 33 fatal cases of eclampsia, noted necrosis and hemorrhage of the adrenal cortex in one-third of the cases. Investigating the clinical picture in these 11 cases he noted that all but two of them died in terminal shock. Of these two patients, one died of pulmonary edema secondary to overhydration for shock and the other died in coma.

The role of the adrenal cortex in obstetrical shock has received more attention in recent years. Mukherjee and Dey,[22] studying the biochemical changes which occur in various stages of shock, found a marked similarity between them and those which occur in the early stages of the general adaption syndrome. Others[23, 24] have reported similar findings. The authors concluded that obstetric shock, whether attended by trauma, blood loss, or severe nervous stimuli, produces a stress that imposes a greater demand on the adrenal cortex and suggest that the manifestations of shock are linked with a relative inefficiency of the cortex which if left untreated may result in exhaustion and acute adrenal insufficiency. This concept is supported by the finding of hemorrhagic necrosis of the adrenal cortex in all of the 5 cases that terminated fatally. Also supportive is Sheehan's[25] investigation of 147 fatal cases of shock without hemorrhage, all of which occurred during abnormal gestations, wherein he noted hemorrhagic necrosis, sometimes grossly visible, of the adrenal cortex.

It can therefore be seen that when the pregnant woman is subjected to these or other stresses, such as abortion,[26] hemorrhage, surgery,[27, 28, 29] prolonged labor,[25] or delivery,[13] greater demands are made upon the already overactive adrenal cortex. In the presence of sensitizing factors such as a nutritional or vitamin deficiency,[30, 31] an inherent weakness, decreased reserve or hypofunction resulting from partial failure of the adrenocorticotropic activity of the pituitary, this reaction may lead to exhaustion of the cortex and acute adrenal insufficiency. Whether the resultant hemorrhage is microscopically or grossly evident seems to depend on factors which at this time are not clear; certainly, the degree of stress itself does not appear to be a factor.

Occasionally, however, other conditions seem to be important as etiological factors. Trauma,[32, 33] hemorrhagic diathesis,[34] compression,[35] and thrombus formation in the adrenal veins[2, 34, 36, 37] are among those that have been implicated. Of these, thrombosis would appear to be more important as reflected in the findings reported by Keele and Keele.[2] That stress may be an added factor in these cases is substantiated by the fact that death may follow unilateral adrenal hemorrhage in spite of the other gland being intact and theoretically capable of maintaining life. Also supportive is the fact that apoplexy has been reported to occur on several occasions following recent contralateral hemorrhage.[2]

Treatment

Whatever the pathogenesis of adrenal apoplexy, prompt and heroic measures are required. Adrenal cortical extracts are the keystone of therapy and are a lifesaving measure if used soon enough and in adequate dosage.[38] The aqueous extract may be given intravenously, 20 to 50 c.c. at a time, every four to six hours. It would appear that at least 200 c.c. daily are required in the early phase of insufficiency.[39] Although the synthetic steroids may be used, 300 mg. cortisone daily and 2 to 5 mg. of desoxycorticosterone, it is felt that these agents do not replace, in over-all effect and rapidity of action, the aqueous cortical extracts.[7] Also, when the synthetic steroids are used, a fine balance must be achieved between inadequate dosage, with resultant failure of therapy, and overdosage where the danger of overhydration and congestve failure looms.

The administration of substantial amounts of glucose, saline, ascorbic acid, thiamine, and pyridoxine potentiates the effects of the cortical extract. It has been shown that their use in conjunction with corticosteroids produces far better results than therapy with corticosteroids alone.[22]

Successful surgical intervention was first performed upon an infant in 1924.[40] Since that time two more cases have been reported in adults.[41, 42] Its place, however, once the patient has been stabilized, is as yet not clear.

Summary

1. Adrenal apoplexy in the adult has been considered a rare finding, only 34 cases being reported in pregnancy. We add one case of our own.

2. Adrenal physiology in pregnancy is discussed.

3. Apoplexy may occur when stress is imposed upon the adrenal cortex already carrying the burden of pregnancy.

4. Adrenal hemorrhage with acute insufficiency may occur during complicated pregnancies more frequently than is realized.

5. The clinical picture of adrenal hemorrhage is outlined and a plan of therapy advanced.

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AN EXPERIMENT IN THE TEACHING OF OBSTETRICS AND GYNECOLOGY AT THE GRADUATE LEVEL

The Application of Clinical Psychiatry in the Teaching of Obstetrics and Gynecology

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SINCE 1948 each Senior Assistant Resident* in this Department of Obstetrics and Gynecology has voluntarily requested and participated in clinical training in psychiatry prior to assuming the duties of Chief Resident in Obstetrics-Gynecology. This has resulted in a five-year teaching experience shared by the Departments of Psychiatry and Obstetrics-Gynecology. Other teachers have expressed interest in this experience which, we believe, may be looked upon as an experiment in graduate medical education. The purpose of this communication is to record our observations so that something may be learned of their positive and negative aspects. Like most experiments, it has both answered and created questions that deal with purpose, methods, and results.

Purpose

Initially the purpose of the first resident who requested psychiatric training was to test a belief that knowledge and experience could be acquired which would permit a more systematic and less intuitive understanding of many obstetrical-gynecological problems. The literature indicates that numerous obstetricians and gynecologists have observed in many patients important clinical phenomena that are unexplained by knowledge accumulated during their traditional specialistic training in morphology, physiology, and pathology. Some are inclined to attribute such phenomena to "psychiatric factors" and attempt to deal with them intuitively. Other clinicians are reluctant to attribute reasons for phenomena they do not understand. In either case, it appears that important limitations of graduate training usually are not appreciated until the clinician has entered private practice, at which time opportunities for continued intensive training seldom exist. An awareness of this within the period of formal training was one factor that led five succes-

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sive residents to request psychiatric training. Each of these residents had been impressed by the inadequacy of the basic sciences to explain many clinical phenomena that each had observed during a year spent as Resident in Charge of the Obstetrical-Gynecological Out-Patient Department. This outpatient assignment has provided special opportunities for a more personal and long-term relationship with individual patients. This opportunity approximates that provided by private practice, and extends the opportunity provided by traditional systems of formal hospital training. Study indicates that the latter tends to consist principally of supervised application of the physical and biological sciences and skills, often applied to a segment of a woman during an episode of lasting importance in her life. The association between resident and patient is relatively brief and is made impersonal, first, by existing hospital departmental organization and, second, by the tendency of the resident to concentrate chiefly upon those aspects of the case necessary to acquire proficiency in specialized diagnosis and in technical skill.

Another important factor in the continuity of this experiment appears to have been the recognition by each resident of the benefits derived by his predecessor from psychiatric training. The teaching experience has been made possible by the Department of Psychiatry in this school and hospital which is closely integrated with other clinical services in both patient care and teaching programs. Although concerned with the training of career psychiatrists through its graduate program, it has devoted equal attention and interest to the education of the medical student and other clinicians. It attempts to present the student with a reasonable knowledge of the basic factors of human nature and of the society in which we live so that, through repetitive clinical experience, the student will become increasingly familiar with the more common and more important emotional problems of his patients.

Method

The obstetrical-gynecological training in this department consists of four years of supervised and traditional clinical experience beyond the intern year. Because of the cardinal importance of pathology, one year has been devoted to the study of pelvic pathology. Although the duties of this assignment are of first importance, they require only a few hours each day. The extra time has been utilized for psychiatric teaching. Thus, added clinical knowledge has been acquired within the framework of an obstetrical-gynecological residency without lengthening the period of formal training and without altering other goals of training in obstetrics and gynecology. In no instance were we dealing with a physician who contemplated a departure from his original objective of becoming an obstetrician and gynecologist. This point was clearly understood by teachers in both departments.

Each of the five residents who participated had had three to four years of hospital training in surgery or obstetrics and gynecology prior to his training in psychiatry. Four had had further experience in the armed services. None had had previous teaching in psychiatry except for a few and relatively in-

effective undergraduate lectures. Four of the five residents were graduates of this school before the current undergraduate program in psychiatry had been instituted.

At the beginning of this experiment, many questions presented themselves to the senior members of both departments. These questions related to objectives, content, and methods of teaching. However, questions could not be answered except by experience. Since, to our knowledge, no such experience has been recorded, it was necessary to proceed slowly and to make observations from which objectives could be accurately defined and methods devised. Consequently, no formal responsibilities within the Department of Psychiatry were assigned to the obstetrical resident. Instead, each has been invited to attend all psychiatric rounds and seminars including those participated in by the medical students. Each has been given the opportunity to study a limited number of patients in the Psychiatric Out-Patient Department. All of these patients had been interviewed and their problems initially appraised by an experienced psychiatrist or psychiatric social worker. For the most part, they have been patients who have recognized the emotional nature of the problem for which they were seen by the obstetrical and gynecological resident. In the choice of patients, attempts have been made to select those whose symptoms were of a type frequently encountered in the practice of obstetrics and gynecology. This included such situations as menstrual disturbances or pelvic pain without demonstrable organic cause, frigidity, dyspareunia, the menopausal syndrome, and emotional reactions precipitated by pelvic surgery. Obstetrical and gynecological residents in psychiatry have also studied a few patients from the Obstetrical and Gynecological Clinic in accord with their own interests. In some instances, these have been patients who had not recognized the emotional nature of their illnesses. Other patients have been seemingly well-adjusted women with organic disease or normal pregnancies.

Historical data have been secured by the obstetrical and gynecological resident from all patients, usually during several interviews over a period of weeks or months. As the data have been accumulated, they have been discussed with an experienced psychiatrist who has been assigned as a personal tutor. Although some psychotherapy is inevitable when patients are seen and personal histories are secured during repeated interviews, emphasis in these discussions has been placed upon methods by which pertinent psychological, social, and medical data may be obtained without unduly disturbing the patient. Furthermore, attention has been directed to the manner by which the acquired data may be interpreted so as to understand the patient more thoroughly and thereby judge more intelligently what diagnostic and therapeutic measures are indicated.

Results

To appraise the results of this teaching experiment, opinions have been collected from each of the residents who have participated. The subsequent relationship of these men to students, patients, and colleagues has been noted

by the authors. Observations have been secured from all full-time members of the obstetrical and gynecological faculty and from certain nurses who have had opportunity to observe closely the chief residents before and during this program. Other observations have been made in the clinics and collected from social workers who have had close contact with the obstetrical-gynecological service. A uniformity of opinion has been found in regard to certain observations. In the presence of significant differences in the observers' perspectives and skills, it is felt that this may reflect a reliable degree of accuracy in these observations.

First, a more concrete appreciation of the value of accurate medical histories as well as increased ability to obtain and interpret meaningful social and psychological data appears to have been gained by each of these residents. This has been manifested by their willingness, despite the demanding duties of chief resident, to devote several hours each week to the discussion of medical histories in order to help medical students improve their ability to acquire and interpret historical data. It has been further manifested by the improved history-taking ability which these residents have themselves acquired. Their histories have contrasted with the tribute which so many clinicians and teachers pay to the importance of medical history while they judge as "noncontributory" or "as recorded" important segments of history that either have not been elicited or have been secured by an inexperienced house officer.

Second, it is believed that during this chief residency each of these men has demonstrated a broader interest in health and disease. Many young men express the value of their residency solely in terms of the number of "cases done." Their interest is at the level of the lesion and may become further restricted to those lesions that are surgically amenable. Each of these residents has shown increased interest in medical and personal problems experienced by patients and in the relationship between these problems and the more restricted pelvic or obstetrical situation. Each has recognized cases in which symptoms were incorrectly attributed to patients as a result of erroneous histories secured by others. Each has encountered and called to the attention of students, residents, and attending staff members cases in which data obtained by his carefully secured history indicated that the symptoms for which an operation had been considered or performed were emotional or medical in nature. The following protocol is submitted as one illustration:

Mrs. G. D., a 62-year-old housewife, was referred because of a cystocele with symptoms of stress incontinence, nocturia, and frequency. Competent urological investigation had been negative. It was noted that she had had a repair and vaginal hysterectomy 12 years before because of similar symptoms. Also, a repair had been advised by a gynecologist one year previously, but had been refused by the patient who was now willing to undergo repair.

Her current symptoms were of two years' duration and dated from the onset of similar symptoms in her husband, who had prostatic hypertrophy. Recently he had had a transurethral resection. It was after this that the patient began to wonder if perhaps she should have an operation. She talked at length about how well he had done and how nice everyone

had been to him. Her past history was one of lifelong hypochrondriasis, the patient frequently having developed symptoms similar to those experienced by relatives and close friends. However, she had led a productive life and had not been incapacitated by these symptoms.

Careful review of her current history indicated considerable disparity between her verbal expression of her symptoms and the degree of disability which she appeared to experience. Upon further questioning she responded with other complaints which she had not offered spontaneously and which seemed to be determined in great part by the questions asked of her.

Examination revealed a cystocele of a degree that would warrant repair if symptomatic, but for which repair was not otherwise indicated.

Because of essential hypertension (170/100) without demonstrable signs or symptoms, she was referred to an internist. The internist chosen was one who was interested in and able to devote adequate attention to her needs. With supportive and reassuring treatment, she has improved and at present, several months later, she no longer complains of bladder symptoms.

Third, because each participant in this teaching experiment subsequently assumed the strategic position of Chief Resident, results observed in each individual have been reflected in other members of the Department of Obstetrics-Gynecology with benefit to the department through: (a) increased interest on the part of the resident staff in the teaching of medical students at a more personal and individual level, (b) the impact on nurses of heightened interest in the physical comfort and psychological welfare of patients, (c) more critical attitudes toward stereotyped concepts, particularly in relation to pelvic surgery, (d) the stimulation of research in areas such as the menopause, pelvic pain, and the problem of symptomatic failure of pelvic repair.

Fourth, the experiment has resulted in a liaison between the Departments of Obstetrics-Gynecology and Psychiatry with the result that each is more familiar with the problems and capacities of the other. It is hoped that this increased communication and understanding may lead to the acquisition of new knowledge through the application of combined skills in investigative problems of mutual interest.

Certain negative observations have been made in regard to the results of this teaching experiment.

Variations have been noted in the degree to which each of these residents has attended and participated actively in psychiatric rounds, seminars, and case studies. Superficially, this variation might be related to the time required by each resident to complete his duties in pathology. However, an experiment like this obviously alerts the participant not only to the emotional problems of patients, but also to his own past and current life experiences. Our desire to learn the motivational interest and capacity of each resident has been another important reason why this experiment was begun and has remained relatively unstructured. A capacity for further growth, previous clinical training, and emotional maturity are necessary prerequisites for training of this type. We believe the resident must be sufficiently self-motivated to want to engage in this experience and that senior members of both departments should make decisions on an individual basis.

We have observed that opportunities to investigate social or psychological data are frequently not taken in the clinic. The role of past or current life experiences in a patient's symptoms or behavior is seldom appreciated except in the general concept that emotional factors might be important. The therapeutic value of the doctor-patient relationship is neither fully realized nor effectively utilized, while the therapeutic value of medicine injected or tissue removed tends to be overvalued. Social service referrals in the clinic are usually limited to requests for social or financial planning in cases of illegitimacy or cases that require hospitalization; the full spectrum of extramedical skills furnished the ambulatory patient by social workers and representatives of other community agencies is seldom appreciated. These are areas in which important gains can be made in the care of patients. It is hoped that favorable changes in these areas will be observed when those who have participated in this program acquire more direct responsibility for the supervision of the resident staff in the care of clinic patients here and elsewhere.

We have also attempted to study the individual experiences of teachers and residents during this five-year period in order to determine those experiences from which the most benefit was derived during the psychiatric training. From this, suggestions have been made for future residents who may elect to share in this experience. These are suggestions which apply to this school and hospital and are not meant to be followed literally in all situations, as the actual method of teaching will depend in great part on the existing interests, personnel, and other teaching facilities:

1. Assignment to a medical floor during the first two months of the Residency in Psychiatry. Here the resident attends rounds conducted by a clinician who is qualified in both psychiatry and internal medicine. Medically ill patients are studied from a medical point of view, and medical problems are formulated and treated. However, adequate personal, social, and family history is acquired to understand the adaptive devices used by the physically ill patient. Inquiry is made into the manner by which these devices may modify the clinical manifestations of the disease and its treatment. Methods are discussed by which such data may be obtained, interpreted, and used within the context of the medical history and the doctor-patient relationship. During this time the obstetrical and gynecological resident has opportunity to interview a medically sick patient and to present the data acquired for discussion. He also participates in the discussion of cases presented by other residents. It is felt that this brief concentrated experience offers excellent opportunities to gain experience with techniques of interviewing physically sick patients and of evaluating psychological aspects of physical illness. This provides a basis for subsequent work on the obstetrical-gynecological service.

2. The resident is assigned to the Obstetrical-Gynecological Clinic one-half day a week where he follows at least one patient during pregnancy, labor, and post partum, one menopausal patient, and one patient before, during, and after surgery for major pelvic disease. Any other types or numbers of patients are followed as the interest of the resident dictates. The supervision of this work is conducted by the assigned tutor in psychiatry and informally by an instructor in obstetrics-gynecology. It is believed that this provides opportunity for the resident to learn something about the emotional experiences of presumably psychologically healthy women during pregnancy, labor, the puerperium, the menopause, and major pelvic surgery.

3. Commencing in the third month of this residency he carries in psychotherapy one patient selected from the Psychiatric Clinic. Attempts are made to choose a patient with symptoms that usually bring a woman to a gynecologist. These include dysmenorrhea, pelvic pain, dyspareunia, sterility, frigidity, etc. The therapy is supervised by an instructor in psychiatry. Here the object is not to develop primarily skills in psychotherapy, but to provide the resident with opportunity to acquire the type of data and knowledge about an individual patient that comes only from a long-term psychotherapeutic relationship.

4. As often as possible the resident attends undergraduate lectures in medical psychology and psychopathology, as well as psychosomatic conferences conducted at a graduate level. During these conferences he presents several of his cases.

5. It is planned to arrange joint meetings between the Departments of Obstetrics-Gynecology and Psychiatry. At these the resident will report on areas of current interest to both disciplines. It is hoped that these may result in mutual stimulation of both departments.

Comment and Summary

We believe that most experienced clinicians will accept the proposition that the obstetrician-gynecologist should have a reasonable knowledge of emotional factors that relate to his specialty together with the capacity to apply the knowledge to the individual patient. Differences of opinion and a surprising lack of specific experience may be expected when one attempts to define, first, what is meant by "a reasonable knowledge of emotional factors," second, how this may best be obtained and, third, what exactly can be done with such knowledge by a clinician who limits his practice to obstetrics-gynecology. Our opinions in regard to each of these points result from the five-year experience that has been studied and described.

First, we believe that the ideally trained obstetrician-gynecologist should be familiar with existing knowledge as to the psychology of acute and chronic illness, of convalescence and disability, of menstruation and the menopause, of pregnancy and sterility, and of the emotional significance of pelvic disease and operations. We believe he should possess the skill in medical interviewing that is necessary to accumulate data by which he can increase this body of knowledge and apply previously acquired knowledge to an individual patient. It is felt that he should possess a systematic understanding of the various relationships that may be established between a doctor and patient together with a conscious awareness of how a particular relationship may be utilized to the benefit of a particular patient.

Second, we do not believe that this knowledge and skill must be derived and applied intuitively during the diffuse cumulative experience of many years in practice. We have observed that through supervised and repetitive clinical experience, basic knowledge of human behavior may be acquired during graduate training. We believe this study has shown that this knowledge can be acquired without lengthening the period or altering other goals of graduate training in obstetrics-gynecology. Reasons for this belief have been presented and consist of the results observed in this experiment. These results have been described and areas for further improvement mentioned.

Third, our experience leads us to believe that knowledge and skills derived from this type of graduate training have multiple values in the practice of obstetrics-gynecology.

Many women without demonstrable anatomic or physiologic alterations experience somatic symptoms that are referred to pregnancy, coitus, and menstruation and anatomically to the bladder, pelvic organs, low back, or abdomen. In a significant number of such patients, symptoms can be understood by social and psychological data that have been adequately secured and correctly interpreted within the framework of a medical history. Similar symptoms are experienced by other women in whom physical alterations are demonstrable. In these cases, the current tendency often is to assume that the pathology is causal to the symptoms, although the relationship may be coincidental and the pathology innocuous. As one example, we have encountered numerous cases in which cystoceles have been repaired by competent surgeons because of bladder symptoms that were emotional in origin. Conversely, we have recognized cases in which symptoms of physical disease have been attributed to "nervousness." Thus, ability to recognize emotional illness with physical symptoms may be utilized to improve obstetrical and gynecological judgment. Ability to recognize only pathology is insufficient.

Because these numerous patients do not, and as a group should not, consult first with a psychiatrist, the obstetrician-gynecologist is in a position to refer for early diagnosis and treatment a significant number of women who may suffer from psychotic or serious neurotic illness. When referral is not possible, recognition of the nature of the illness may at least prevent operative or other ill-advised treatment. Hence, this diagnostic skill may also be utilized in an important preventive manner.

However, diagnostic skill alone may be inadequate to meet the therapeutic demands of some patients. Therefore, the question of what the ideally trained obstetrician-gynecologist can and cannot do in the psychotherapeutic treatment of emotionally disturbed patients is a question that we have studied. It is a fact that there is an insufficient number of trained psychiatrists to treat adequately all patients who are emotionally ill. Furthermore, some patients who are seriously disturbed may be unable to accept consciously or to tolerate emotionally intensive and direct psychotherapy. By contrast, emotional disturbances of other patients are transient and may be due to realistic problems that do not require special psychotherapeutic skills. Despite these facts, some clinicians, either by preference or conviction, may refuse to treat problems that are not within the rigid limits of their specialty. In this regard, we call attention to the fact that whatever the clinician says or does not say, as well as the setting in which this occurs, may have special psychological meaning to a disturbed woman and may, therefore, have negative or positive psychotherapeutic value. Because of these considerations, we not only believe that the obstetrician-gynecologist should engage in psychotherapy, we believe that he does so inevitably and that it is preferable for him to do this with some degree of awareness rather than intuitively or unknowingly. When formal psychotherapy

by a trained psychiatrist is not feasible, our experience has been that physical symptoms may be treated by medications or physical methods that are not likely to do physical or psychological harm. After a confident relationship has been established, the obstetrician-gynecologist is then in a strategic position to reassure the patient that no significant physical abnormality exists and to deal directly, through discussion or manipulation of the environment, with those emotional problems that are current, conscious, and realistic. We strongly believe that attempts to elicit and to deal directly with unconscious material are incompatible with the practice of obstetrics-gynecology and should be left to the trained psychiatrist. However, the clinician or investigator with some knowledge of unconscious processes and psychological adaptive devices is in a position to observe clinical phenomena more intelligently and thereby contribute to his understanding of the patient and perhaps to our body of knowledge.

In many fields of applied science there is a tendency, perhaps inevitable, to think in terms of stereotyped concepts. In gynecology this tendency is illustrated by our preconceptions of the nature of distress associated with the menopause, hormonal imbalance, anatomic pelvic relaxation, and various types of pelvic pathology. It appears that toward these stereotyped concepts the participants in this experiment have acquired a more critical attitude, the continuation of which may encourage more intelligent surgery and promote more meaningful clinical observations.

Last, we have found that the increased understanding of human behavior may be utilized to effect a more mature recognition of medical limitations with the result that the younger clinician is made less anxious by his inability to cure every symptom and is therefore less likely to become disturbed in his relationship toward certain types of patients. He may be less likely to manipulate facts to fit traditional concepts and speculative theories or to employ, as a manifestation of his own anxiety, major surgical procedures to deal with physical symptoms that he may suspect are emotional but which he otherwise does not know how to "cure."

Since the end of World War II this and other medical schools have inaugurated expanded programs of psychiatric instruction during the undergraduate years. It may be that students who have received this instruction will not need and therefore will not benefit from graduate experience in psychiatry to the degree currently observed. However, part of the results we have noted are undoubtedly related to the maturity and clinical experience acquired by each participant before his residency in psychiatry. It is possible therefore that future obstetrical residents who have had basic undergraduate instruction in psychiatry will have a foundation from which even greater benefit may be derived from supervised psychiatric training after they have secured a broad graduate clinical experience. It is hoped that this will be a subject for future study.

Department of Case Reports
New Instruments, Etc.

THREE CASES OF LATE PUERPERAL HEMORRHAGE CAUSED BY PLACENTAL POLYP

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ONE of the rarer causes of late puerperal hemorrhage is the so-called placental polyp. Such polyps are "composed of placental tissue which may remain in the uterus for many years following pregnancy" (J. I. Brewer[1]). Greenhill[2] found "a piece of placenta which had remained in a fibromyomatous uterus for eighteen months, and Riess found placental villi in uterine vessels eighteen years after the last delivery."

Through deposition of fibrin and partial organization thereof, a polypoid mass of varying size may grow within the uterine cavity, giving rise to symptoms of bleeding of any character, and of cramplike lower abdominal pains. Infection may complicate the picture. One such case was discussed from the case records of the Massachusetts General Hospital, where the differential diagnosis rested between tubovarian abscess and infected ectopic pregnancy.

Careful review of the available recent literature yielded scant information on this subject. Other than the case referred to, only a few more reports were encountered. Hagstrom[3] recorded a placental polyp causing life-threatening hemorrhage, removed by supracervical hysterectomy. More recently Kanatser[4] reported a case in which vaginal bleeding of a year's duration was caused by a placental polyp. Dorsey[5] and Magney[6] both report one case each of placental polyp simulating chorionepithelioma.

It is because of this relative paucity of cases, and our impression that placental polyps give rise to a distinct early history which is almost pathognomonic, that we are reporting three cases of placental polyp observed at the Margaret Hague Maternity Hospital in fairly recent years.

These three cases probably do not represent the actual incidence of placental polyps at our institution. Several members of our Staff seem to remember that similar cases occurred without being able, however, to identify them positively. Moreover, as Novak[7] states, a fair number of placental polyps undoubtedly are passed spontaneously.

The following three case histories are recorded from this Clinic:

CASE 1.—Mrs. E. P., No. 71447, a 29-year-old gravida i, para 0, was admitted to the Margaret Hague Maternity Hospital on March 23, 1947, at 37 weeks' gestation, with a history of premature rupture of the membranes, and pinkish vaginal discharge of three hours' duration.

The past history was noncontributory. Her antepartum course was uneventful until the eve of the day of her admission when in the course of a rectal examination at her doctor's office, she passed two ounces of bright red blood vaginally.

On admission to the delivery floor, she had a blood pressure of 142/86, no edema, and no proteinuria. The uterus was somewhat tense, and irritable, but there was no bleeding at the time. The vertex was floating, and the fetal heart was regular in the left lower

quadrant. Because of the history of vaginal bleeding, no rectal examination was done. One hour following admission, labor commenced, and passage of clear amniotic fluid was seen. Labor continued satisfactorily, and eighteen hours later, under 50 mg. Novocain spinal anesthesia, supplemented by nitrous-oxide-oxygen-ether anesthesia, a living male child was delivered through succession of Kielland and Dewees forceps applications. Pitocin, 1 c.c., was given intramuscularly immediately after delivery of the child, and the placenta was removed manually four minutes later. On inspection, the latter was thought to be complete. Ergotrate, 1 c.c., was given four and twenty minutes later, respectively. A second-degree perineal and a slight periurethral laceration were repaired. The total blood loss was estimated at 600 c.c., for which the patient received a transfusion of 500 c.c. of whole blood.

Apart from a secondary anemia (red blood count 3.2 million, hemoglobin 8.9 Gm.) and rather severe and persistent afterpains, the postpartum course remained uneventful. She was discharged on the ninth postpartum day, with the uterus apparently well involuted, but discharging a moderate amount of lochia rubra.

The lochia continued red for the next eighteen days. On the thirtieth postpartum day, the flow became more profuse and continued to remain so until her readmission on the thirty-fourth postpartum day, June 25, 1947.

On readmission, temperature was 100° F.; pulse 84; red blood count 3.57 million, hemoglobin 9.9 Gm. Vaginal examination done in the operating room showed the uterus to be slightly enlarged, boggy, with the cervical canal patent and easily admitting one finger. Just above the internal os there was felt a globular, smooth mass the size of a plum, seemingly attached to the fundus. A diagnosis of placental polyp was made, the latter grasped with a sponge forceps, and twisted off at its base. Subsequently, a curettage was done, and the patient was given 500 c.c. of whole blood. Sulfadiazine therapy was instituted. The patient had an uneventful recovery, and left the hospital on the third postoperative day.

Pathological Report.—The specimen consisted of 5 grayish hemorrhagic, firm pieces measuring from 1 to 5 cm. in diameter. Cross section showed hemorrhagic, spongy villouslike tissue. Microscopic sections showed mostly thin villi in process of regression with marked necrosis and hyalinization, many of them still showing epithelium and extensive hemorrhage.

Diagnosis.—Necrotic placental tissue.

CASE 2.—G. K., No. 122214, a 30-year-old white gravida iii, para ii, at term, was admitted to the labor floor of the Margaret Hague Maternity Hospital on Jan. 20, 1952, at 3:00 A.M., in active labor. The membranes had ruptured at the onset of labor two hours prior to admission.

Findings.—The blood pressure was 120/84. The cervix was one finger dilated, the membranes ruptured, and the vertex was presenting at minus one station in right occipito-transverse position. The fetal heartbeat was regular in the right lower quadrant.

The past medical and surgical histories were negative. The past obstetrical history showed a normal spontaneous delivery in 1943; a premature labor and delivery with neonatal death and postpartum hemorrhage, necessitating transfusion of 500 c.c. of blood and curettage three hours post partum in 1947.

The antepartum course was marked by threatened abortion at 15 weeks' gestation, and ptyalism.

After a total of eleven hours of labor, the last four of which were stimulated with fractional doses of Pitocin, the patient was delivered, without difficulty, with the use of Kielland forceps. However, immediately following delivery of the baby, there was an excessive amount of bleeding. The placenta was removed manually, and thought to be complete. One c.c. of Ergotrate was given intravenously, and another intramuscularly, five and eight minutes following delivery, respectively. Bleeding was controlled, and a median episiotomy was repaired.

The patient was discharged seven days post partum, with the fundus four finger-breadths above the symphysis and discharging a moderate amount of lochia serosa, after an afebrile postpartum course characterized by strong afterpains.

For the following month, the patient continued to have daily vaginal bleeding, associated with cramps and passage of clots. On the thirty-seventh postpartum day, she was started on Ergotrate, 1/320 grain three times a day for seven days. When the bleeding became more severe, she was readmitted to the hospital on the forty-third postpartum day.

On admission, physical examination was essentially negative, except for some old blood on the vulva. The hemoglobin was 78 per cent, 11.3 Gm., and the red blood count was 4.04 million. Vaginal examination showed "patulous cervix with the uterus twice normal size, with a submucous fibroid measuring 2 inches long and 1½ inches at the base projecting from the superior wall of the uterus."

A dilatation and curettage were done, and the cavity "loosely curetted. A moderate amount of hyperplastic endometrium was obtained." (Pathological report later was "acute decidual endometritis.") The estimated blood loss was 500 c.c. A uterine pack was inserted, and left in place. The patient received a transfusion of 1,000 c.c. of whole blood, followed immediately by a rise in temperature to 104° F.

Thirteen hours later, because of further bleeding and the presumed uterine tumor, a total abdominal hysterectomy and appendectomy were done under spinal anesthesia, through a Pfannenstiel incision. On opening the uterus, it was found to contain a piece of placenta measuring 5½ cm. in diameter. The postoperative course was uneventful. On the second postoperative day, the red blood count was 4.65 million and hemoglobin 93.9 per cent. The patient was discharged on the tenth postoperative day.

Pathological Report.—

Gross: The uterus with cervix separately and no appendages weighed 185 grams. The serosa was smooth. The uterine cavity was distended and lined by hemorrhagic soft endometrium. There was a round nodule hanging from the fundus measuring 6 cm. in diameter, firm, crumbling, and hemorrhagic; it broke off easily from the fundus leaving tags. The wall averaged 3 to 4 cm. thick. It was fibrotic, raglike. The cervix had a skinlike covering, but the wall was thin and fibrotic.

Microscopic: Section of the nodule showed ghosts of villi. There was extensive necrosis and marked hyalinization at the periphery with fibrosis of some of the villi. Several sections of the base showed marked hyalin degeneration with scattered outlines of decidual cells. Only at the border were involuted glands seen. The entire uterine wall showed irregular fibrosis with dilated large blood vessels, some completely thrombosed with thick hyalinized walls and obliterated lumen. Section of cervix showed normal squamous epithelium and irregular fibrosis.

Microscopical Diagnosis.—Marked fibrinoid degeneration of the placental site, with placental polyp. Chronic metropathy.

CASE 3.—J. W., No. 122152, a well-developed, well-nourished 25-year-old white gravida iii, para ii, was readmitted to the hospital thirty-two days post partum because of late puerperal hemorrhage.

Her past history was noncontributory.

The present pregnancy was uneventful until Jan. 29, 1952, when desultory labor commenced and continued for eighteen hours at home. Two hours following admission, normal spontaneous delivery occurred. One c.c. of Ergotrate was given intravenously after delivery of the head, and the placenta was expressed three minutes later. Shortly thereafter, the patient had an episode of bleeding which stopped after an intravenous infusion of Pitocin. She was allowed out of bed on the second postpartum day, but was returned to bed on the third day because of passage of clots. She was transfused twice for secondary anemia. She was discharged on the tenth postpartum day, apparently in good condition.

Following discharge, the patient continued to have daily passage of small clots, accompanied by intermittent cramping pains. Five days prior to admission, the cramping became worse and she felt feverish. The day before admission, she passed two large clots with severe cramps, and an Ergotrate series was started. The next morning, because of persistent bleeding, readmission was advised.

Findings on readmission were restlessness, apathy, pallor, and fever of 101° F. The uterus was palpated 2½ fingerbreadths above the symphysis, and was tender to palpation. The red blood count was 3.1 million, and the hemoglobin 8.7 Gm. (60 per cent). There was a mild microscopic pyuria.

The fever reached 102.4° F. the night of admission, and she was treated with aureomycin and two small transfusions (250 c.c. each) for the first two days. On the second hospital day, a speculum examination showed an open cervix with a piece of placental tissue presenting in it.

The following day, the patient was taken to the operating room, and the placental tissue which was still adherent to the uterus was digitally removed. A curettement was also done. Another 500 c.c. of blood was given.

Following operation, the temperature immediately dropped to normal and remained so. Aureomycin was continued for three days. On the fourth postoperative day, the red blood count was 3.96 million, and hemoglobin 10.7 Gm. (74 per cent), and lochia had practically ceased. The patient was discharged in good condition that same day.

Pathological Report.—

Gross: The specimen consisted of 3 c.c. of tissue fragments 1 to 3 cm. in diameter with membranous structure.

Microscopic: Section showed extensive necrosis and hemorrhage; some villi were hyalinized with little epithelium and no blood vessels.

Microscopical Diagnosis.—Necrotic placental tissue.

Comment

There are a number of notable similarities in the three cases presented. In all there were an afebrile early postpartum course, severe afterpains, and severe hemorrhage from one to one and a half months post partum. In two cases clots were passed repeatedly while the patients were still in the hospital, and in two of the three the third stage was forcibly shortened by manual removal of the placenta before normal third stage uterine activity had commenced.

Two patients were cured by curettage. One had a hysterectomy following a timid attempt at digital removal and curettage, the operator's attitude probably resulting from his conviction that he was dealing with a submucous fibroid. The pathologist subsequently proved not only the true nature of the polyp, but also the fact that it broke off easily and could, therefore, have been removed vaginally as were the others.

The differential diagnosis should consider decidual endometritis with subinvolution, submucous fibroid, endometrial hyperplasia, and chorionepithelioma. Where the patient has been taking diethylstilbesterol, endometrial hyperplasia is strongly suggested. Of chorionepithelioma Novak writes, "The gross appearance of the placental polyp together with its grumous hemorrhagic appearance is not unlike that of chorionepithelioma, and I know of several instances in which such a diagnosis was made in spite of the totally different microscopical structure of the two lesions." The cases of Dorsey and Magney rather forcibly emphasize this point.

Therapy of this condition should rely upon prevention rather than correction. Prevention consists of conservative management of the third stage of labor, systematic inspection of the placenta, and exploration of the uterine cavity where indicated. Inspection of the placenta must be thorough, and the possibility of succenturiate lobes kept in mind. An apparently intact placenta is no absolute guarantee against retention of fragments. Exploration of the uterine cavity is indicated whenever a placenta is removed manually, or when it presents a ragged appearance. When there is excessive postpartum

bleeding, exploration is mandatory. Careful attention to the fundus and lochia should always be paid during the early postpartum period and *persistent passage of clots with afterpains should be regarded as an indication for curettage.*

Treatment of placental polyp, when present, consists of correction of the anemia, treatment of infection, and removal of the polypoid mass with subsequent curettage. Hysterectomy is rarely indicated unless adequate surgery fails or the uterus is irrevocably damaged.

Summary

1. Three cases of placental polyp are detailed and reviewed.

2. The pertinent literature has been reviewed.

3. The data considered significant for diagnosis are recorded, and the effective therapy noted.

4. Means for effective prevention are considered, with late surgical therapy described.

5. Hysterectomy, with rare exceptions, is not indicated.

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DYSGERMINOMA OF THE OVARY

A Review of the Literature and a Report of Two Additional Cases

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DYSGERMINOMA of the ovary is a malignant tumor lacking hormonal effects, characterized by no signs and symptoms other than those of an enlarging pelvic neoplasm. To date about 450 cases have been reported in the world literature. We are herewith adding two more cases—one with an apparent favorable outcome 8 years after surgery.

The problem of histogenesis is still unsettled. Meyer first used the term *Dysgerminoma* in 1931 for a tumor resembling the seminoma of the testicle. Many investigators believe it to be a counterpart of the testicular seminoma although spermatogonia do not occur in the ovary. This tumor frequently has been associated with hermaphrodites or pseudohermaphrodites, although many cases have been reported associated with pregnancy, before, during, or after surgery. The histopathologic picture is that of a Grade IV embryonal carcinoma lymphoid stroma. Ewing regarded the tumor as an atypical teratoma. The absence of hormonal effects associated with the tumor is consistent with the neutral character of the undifferentiated cells comprising its histogenetic picture.

Dysgerminomas are considered a Grade IV malignancy, yet the degree of malignancy varies with each case. There is no apparent correlation between the histologic picture of a dysgerminoma and its degree of malignancy, for paradoxically if the neoplasm is unilateral, remains encapsulated and nonadherent, without ascites, a relatively good clinical prognosis may be predicted. Mueller and associates[1] reviewed 427 cases of dysgerminoma of the ovary in 1950 and found a 27 per cent survival rate at the end of 5 years and almost 5 per cent at the end of 15 years. Of the patients who died as a direct result of the tumor, 75 per cent succumbed in the first year after surgery.

The tumor has been classified as radiosensitive by numerous authors, including Dockerty,[2] and Novak.[3] Russo and Kelso[4] in 1949 reported the case of a woman with pulmonary metastases who survived seven and one-half years after surgery followed by radiation and the administration of male sex hormones for a two-year period.

The actual degree of malignancy of these tumors depends primarily upon the findings at surgical exploration. The presence of local or general metastases, as well as hemorrhagic ascites, ruptured capsules, twisted pedicles, or bilateral tumors bodes ill for a favorable outlook. If no further metastases occur after one year, the outlook is materially improved. Metastases have been reported to nearly every organ in the body but most frequently to the pelvis, retroperitoneal nodes, kidneys, and lumbar spine. The mode of spread is said to be primarily lymphatic. Mediastinal and pulmonary extensions have been noted similar to those accompanying testicular seminomas.

Clinically these tumors have no characteristic findings. The age range has varied from 2 to 78 years, with about 73 per cent of the cases occurring between 11 and 30 years of age. The tumors are reportedly found on the right side in approximately 50 per cent of the cases, 35 per cent on the left, and 15 per cent bilaterally. Mueller and co-workers[1] at Kings County Hospital reported that 1.1 per cent of all ovarian neoplasms, solid or cystic, were dysgerminomas over a period of ten years.

Hormonal studies usually yield negative results since the tumors are composed of fetal gonadal tissues prior to sex differentiation. Most cases are diagnosed by surgical exploration

for signs of a pelvic mass with pressure symptoms. Those cases which have local or general metastases reveal clinical pictures of the spreading lesion. Usually a fairly large pelvic mass is palpable. The tumors may be small, but often grow to large size and eventually arise out of the pelvis. The tumor is usually like a dermoid cyst, but may become cystic, particularly if torsion of the pedicle takes place. Ascites occurs in about 15 per cent of the cases and is a bad prognostic sign, especially if hemorrhagic.

The treament of dysgerminoma of the ovary is surgical as well as roentgenological. If the tumor is unilateral and encapsulated without ascites and the opposite tube and ovary are normal, a unilateral oophorectomy is indicated. Should bilateral tumors be found, with or without extension, radical surgery is the procedure of choice followed by irradiation. A total hysterectomy and bilateral salpingo-oophorectomy are recommended. When conservative surgery is done, particularly in women in whom the preservation of the childbearing function is desirable, frequent and regular pelvic examination should be done afterward. Deep roentgen therapy is reserved for recurrences. Since the tumor is radiosensitive, some encouraging results have been reported. The case of Russo and Kelso[4] with its response to testosterone for two years is interesting and has undoubtedly opened a new therapeutic approach particularly in the event of metastases.

Pedowitz and Grayzel[5] recommend radical surgery in those patients who have children or who are postmenopausal.

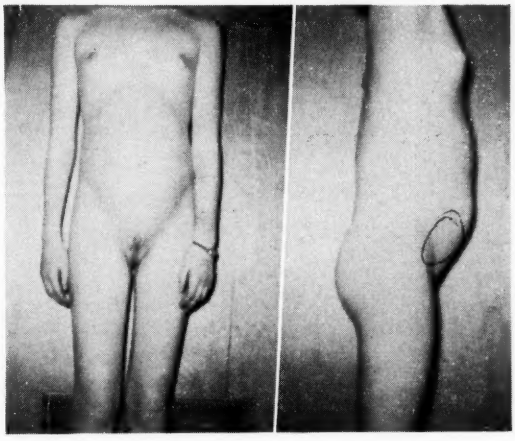


Fig. 1. Fig. 2.

Figs. 1 and 2.—Photographs of Case 1 on first admission to hospital, Jan. 23, 1950.

CASE 1.—This is the case of a white girl, J. H., aged 13 years, who was admitted to Doctors Hospital on Jan. 17, 1950. This girl was first seen at home on January 16 with a chief complaint of lower abdominal pain of about eighteen hours' duration. She had been a normal-appearing and developing child until November, 1949, when she fell down while playing at school. Following the injury she complained of recurrent and intermittent abdominal distress not associated with meals, and she noticed a slight enlargement of the lower abdomen for the preceding two months. There was no nausea, vomiting, or change in bowel habits. Past medical history included a tonsillectomy and adenoidectomy. There was no history of serious illness or accidents. She was the second of three children, all of whom had been delivered and had developed normally. The mother and father were alive and well. She had had considerable dental trouble for the past two years. She had not yet begun to menstruate.

Examination revealed a well-developed, well-nourished, preadolescent white girl who appeared distressed but not acutely ill. She was pale, had an anxious facies, and a rounding of the lower abdomen from the umbilicus to the pubis. Her temperature was 100.4°F. The upper central incisors were ridged and had a brownish pigment deposited in the ridges. The

tonsils had been removed. Examination of the heart, lungs, and extremities was normal. The abdomen was rounded and there was a slight amount of breast development. There was a sparse growth of pubic hair. The external genitals were normal. There was a hard, solid mass arising in the lower abdomen and extending to the umbilicus. This mass moved with respiration and extended into the right flank. There was a shifting dullness to percussion. From the right flank the mass felt nodular and extended to the hypogastrium. In the left lower quadrant the mass felt smooth and soft. Liver and spleen were not palpable. Rectal examination revealed the presence of fullness in the pelvis. The impression on admission was a mass of renal or right ovarian origin. X-ray examination revealed an elevated diaphragm and a bilateral pressure hydronephrosis, due to a large soft-tissue pelvic mass in the anterior peritoneal cavity. Radiographs of the skull and chest were normal.

Fig. 3. Fig. 4. Fig. 5.

Figs. 3 and 4.—Radiographs of the abdomen (anterior-posterior and lateral views) illustrating the presence of an intra-abdominal mass displacing the intestines to the right side of the abdomen and cephalad.

Fig. 5.—Excretory urogram illustrating pressure on both ureters producing bilateral hydronephrosis.

On admission the hemoglobin was 9.5 Gm. with a red blood count of 3.62 million. The white blood count was 8,800, with a normal differential. The urinalysis, nonprotein nitrogen and serologic test were negative. The temperature was elevated most of the time and ranged from 99.6° to 100.4°F. Except for mild pressure symptoms the patient remained fairly comfortable. A laparotomy was delayed for transfusions to correct the secondary anemia. On Jan. 24, 1950, under general anesthesia, the abdomen was entered through a right paramedian incision. On opening the peritoneal cavity a large amount of hemorrhagic ascites was encountered and removed by suction. There was a large cystic mass replacing the right ovary and this mass had ruptured through its capsule. There were numerous transplants with a tremendous amount of sloughing and degeneration of the mass which had undergone torsion of its pedicle. Portions of the tumor were lying free in the ascitic fluid. The patient went into deep surgical shock and suffered a vascular collapse, so that the operation was terminated after the right tube and ovary were removed and an attempt was made to remove the free floating pieces of tissues. One cigarette drain was inserted into the cul-de-sac and the abdomen was closed. A cut-down transfusion was done on the right ankle. Her course was stormy for several days and she was given postoperative transfusions. She was discharged on the eleventh day after surgery in fairly good condition.

She was referred for deep x-ray therapy shortly thereafter and received treatments up to March 14 when the hemoglobin fell to 6.5 Gm. and she was readmitted to the hospital where she received 250 c.c. of whole blood daily for four days. She had begun to exhibit signs of intraperitoneal metastases, especially to the liver, and in spite of supportive therapy her course was rapidly downhill. She died at home on April 15, 1950. Postmortem was denied.

Fig. 6.

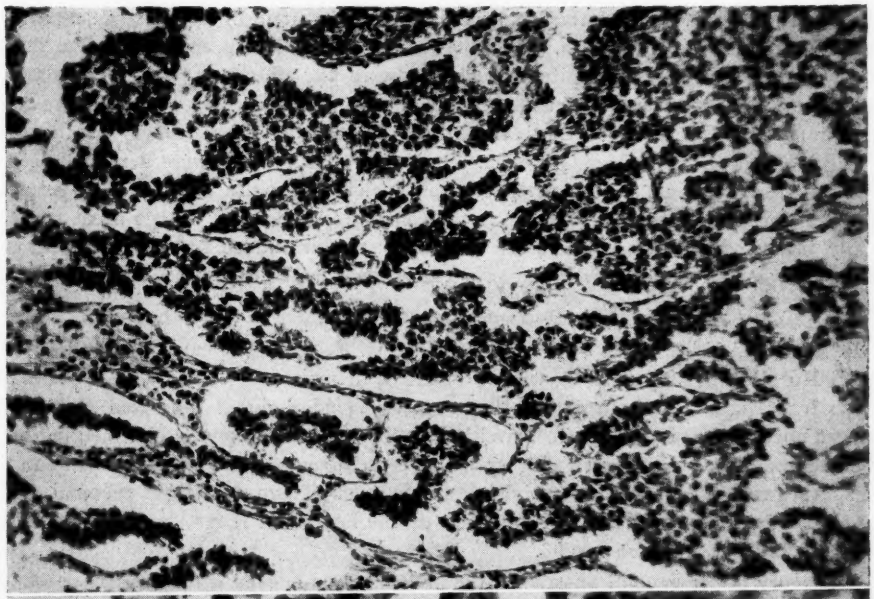
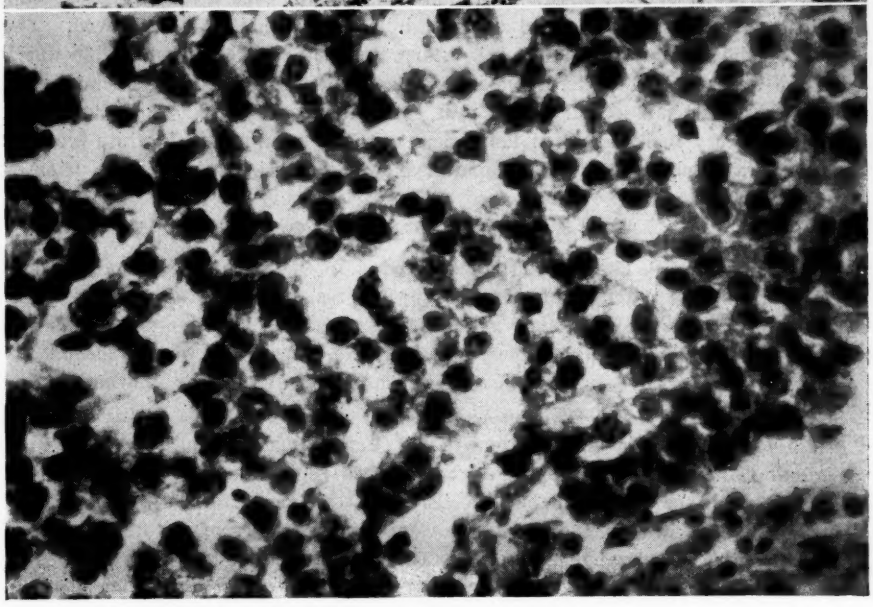


Fig. 7.



Figs. 6 and 7.—Low- and high-power photomicrographs of tumor removed from Case 1, showing a lymphocytic infiltration of the stroma and the sheetlike strands of tumor cells.

Gross Examination.—The specimen was an ovoid-shaped, partly encapsulated mass weighing 1,000 grams and measuring 16 by 13 by 7 cm. The surface was lacerated on one side and friable gray-brown tumor tissue was protruding. Attached to the surface was a Fallopian tube

which measured 4 cm. long. The fimbriated end was patent. The thickness was 0.3 cm. No gross abnormalities were seen and the consistency was rubbery. The cut surface was made up of a gray-white and, in area, gray-pink tissues without any definite pattern. There were areas of cystic degeneration and necrosis.

Microscopic Examination.—Sections showed complete absence of a normal ovarian parenchyma. The latter was replaced by a very cellular tumor which presented a characteristic alveolar pattern. Solid nests of tumor cells were embedded within various-sized strands of loose connective tissue. The latter was extensively infiltrated by lymphocytes. The tumor cells were large and quite uniform. The nuclei was ovoid, rich in chromatin, and frequently displayed numerous nucleoli. Quite remarkable were the abundant, very irregular mitotic figures. The cytoplasm was rich in amount, in many instances eosinophilic, in others vacuolated. The previously described alevolar pattern was lost at the periphery of the tumor in some places, due obviously to compression. Strands of tumor cells were arranged in a sheet-like fashion. In addition, at the periphery the nuclei were quite frequently hyperchromatic and mitoses were more pronounced than at the center of the tumor. Large areas were hemorrhagically infarcted. In some places the neoplasm was surrounded by a broad tissue capsule. In most areas, however, the growth had penetrated through the capsule. We were dealing here with a malignant dysgerminoma.

CASE 2.—This is the case of a white woman, H. J., aged 17 years, who was admitted to Mt. Sinai Hospital on May 8, 1944, with a diagnosis of acute appendicitis. She had had right lower quadrant pain twelve to sixteen hours prior to admission. This was associated with nausea but no vomiting or change in bowel habit. No other history was obtained on admission because she was taken directly to surgery as an emergency case. The initial examination revealed spasm present over the lower right rectus muscle. There was slight rebound tenderness but no signs of a mass present. Examination of the heart and lungs was normal. The blood pressure was 120/80, the pulse was 96.

At surgery under general anesthesia the abdomen was opened through a right paramedian incision. The surgical note indicated that an inflamed appendix was removed. There was also a mass of the right ovary which was interpreted as a dermoid cyst. This was likewise removed. She was returned to her room in good condition and following an uneventful postoperative course was dismissed on the seventh postoperative day. The laboratory findings on the day after surgery included a red blood count of 4.33 million and a white blood count of 18,500. There was a slight polychromatophilia and anisocytosis present. The urine examination was negative.

The pathological report of the removed specimens was as follows:

Gross Examination.—The appendix measured 4.5 by 0.5 cm. The serosa was not injected. The lumen was patent and empty. The mucosa was edematous. In addition there was present an oval-shaped, encapsulated tumor measuring 6.5 by 5 by 3 cm. It had a doughy consistency and a slight nodular surface, gray pink in color; the cut surface had a glassy, finely nodular, yellow-gray appearance. There was gross evidence of normal parenchyma.

Microscopic Examination.—Numerous sections, taken from the cystic tumor, showed almost complete absence of ovarian parenchyma. Very occasional follicle cysts and a rather large germinal follicle were seen. There was uniform replacement of the stroma by masses of large, round, ovoid, or polygonal-shaped cells which were characterized by an abundant clear cytoplasm and heavily stained nuclei. There were large numbers of mitotic figures. Characteristic was the alveolar arrangement of the cellular masses. They were grouped in nests, separated from each other by broad bands of hyalinized connective tissue which was extensively infiltrated by lymphocytes. Toward the periphery the cells were frequently arranged in long columns or strands. The stroma was in most areas loose and edematous and equally infiltrated by lymphocytes. Frequently tumor cells penetrated into lymph spaces. The tumor was surrounded by a thin connective capsule which was in some areas invaded by cellular aggregates. The picture was that of dysgerminoma. The mucosa of the appendix was infiltrated by neutrophilic leukocytic cells. The serosal coat showed clusters of invading tumor cells.

Diagnosis.—Dysgerminoma of the left ovary (embryonal carcinoma) with metastases to the appendix. Acute catarrhal appendicitis.

This patient was given x-ray therapy to the abdomen but refused to cooperate and discontinued her treatments after approximately four or five had been given. She was contacted in 1952 at which time she was alive and well and married. She has never been pregnant.

Conclusions

1. A review of the literature on dysgerminoma is given.

2. Two cases, one with an apparent cure after eight years following surgery, are added to the literature.

We are indebted to Dr. D. H. Lando, Jr., for the presentation of Case 2.

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CARCINOMA OF THE OVARY WITH MALIGNANT CELLS IN THE VAGINAL SMEAR OF AN ASYMPTOMATIC PATIENT*

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IN 1949, Frech[1] described a carcinoma of the ovary with malignant cells in the patient's vaginal smears. The infrequency of this finding is indicated by the sparsity of subsequent similar articles.[2-4]

This is the case of a Navy nurse who, although without symptoms at the time of her annual physical examination, was found to have vaginal smears containing malignant cells from an adenocarcinoma of the ovary which did not become clinically manifest until months later.

Case Report

The patient, a 35-year-old Navy nurse, was completely asymptomatic at the time of her annual physical examination on Nov. 27, 1951. Thorough routine physical and roentgenographic examinations at that time disclosed no abnormalities but cytologic study of the vaginal secretion revealed the presence of malignant cells (Figs. 1 and 2). Repeated pelvic examinations failed to reveal any positive findings, but cervical conization and endometrial curettage were performed on the basis of the positive cytologic report. While the patient was under anesthesia, the pelvic organs were carefully palpated and again no abnormal masses were detected. Histological study of the tissue disclosed only mild chronic cervicitis. Subsequent cytological examinations of vaginal and cervical secretions were negative for malignant or suspicious cells.

On Feb. 5, 1952, the patient was readmitted with signs and symptoms of massive right pleural effusion. Several liters of blood-tinged, straw-colored fluid were aspirated during the next few days. This fluid was found to contain malignant cells similar to those which had been present in the vaginal secretions (Fig. 3). At the suggestion of the pathologist, attention was directed toward the ovaries and a pelvic examination four days later revealed an irregular, indefinite mass in the region of the left ovary. A small amount of peritoneal fluid was also noted and within a few days severe ascites developed. On Feb. 15, the abdomen was explored. The peritoneal cavity contained about 4 L. of blood-tinged yellow fluid which teemed with bizarre, malignant cells (Fig. 4). The left ovary, which was adherent to the left cul-de-sac, was partly replaced by a friable neoplasm which by frozen section examination was found to be adenocarcinoma. Small metastatic nodules were seen on the peritoneal surfaces of the right ovary, Fallopian tubes, uterus, bowel, and within the greater omentum. No masses were seen or palpated in the biliary or gastrointestinal tracts. Panhysterectomy and omental resection were performed.

The patient's immediate postoperative course was satisfactory but she returned one month later with recurrence of the effusions. She was transferred to the Brookhaven National Laboratory Hospital where 18.0 Gm. of radioactive ammonium chloride were instilled into the peritoneal cavity within a period of one week. Attempts to inject similar material into the pleural cavities were unsuccessful. Despite these procedures there was gradual reaccumulation of fluid, the patient's course was steadily downhill and signs of incomplete bowel obstruction ensued. Death occurred on April 15, 1952. An autopsy was performed.

*The opinions or assertions contained herein are those of the writers and are not to be construed as official or reflecting the views of the Navy Department or of the naval service at large.

Fig. 1.

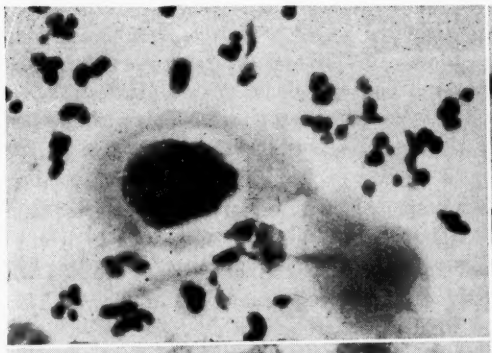


Fig. 2.

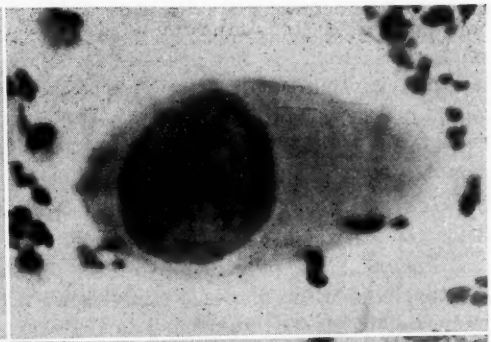
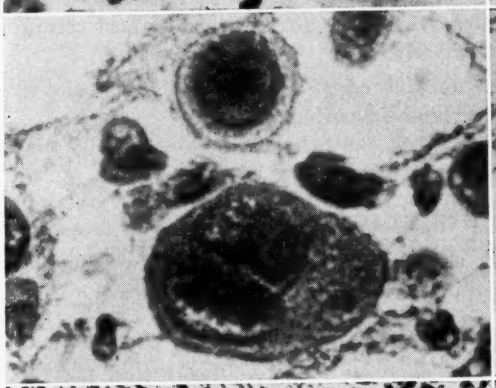


Fig. 3.



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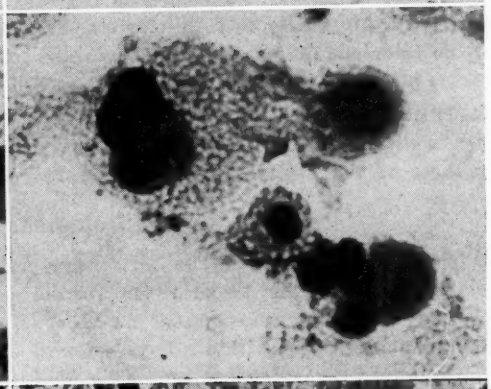

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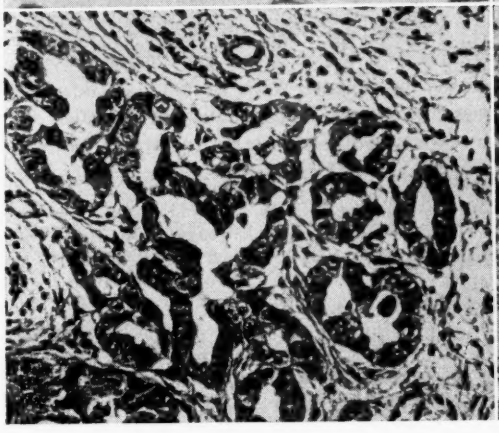

Fig. 6.

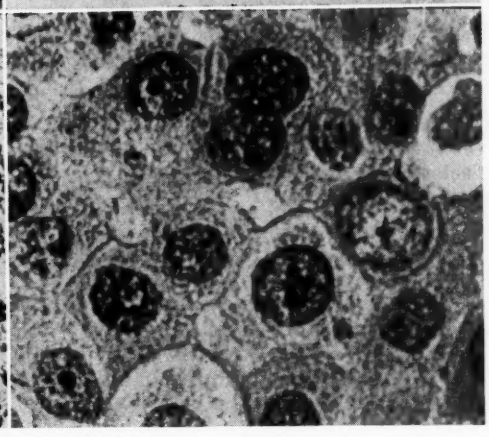

Fig. 1.—Vaginal smear. Large malignant cell showing a prominent nucleolus, irregular nuclear borders, increased chromatin, perinuclear halo, and abundant pink cytoplasm. (×580.)

Fig. 2.—Vaginal smear. Malignant cell with giant nucleus and irregularly clumped chromatin. (×580.)

Fig. 3.—Pleural fluid cell block. Two malignant cells. Compare the one in the upper center with those in the histologic section in Fig. 6. (×660.)

Fig. 4.—Peritoneal fluid smear. Cluster of degenerating malignant cells. The massive cell in the upper left is multinucleated with giant nucleoli. (×660.)

Fig. 5.—Histological section of left ovarian tumor showing adenocarcinoma. (×150.)

Fig. 6.—Higher magnification of the carcinoma. Note the resemblance of the cells to those seen in the smears. (×660.)

Cytological Examinations

Vaginal Fluid (Figs. 1 and 2).—The smears contained innumerable bizarre cells with large nuclei and abundant cytoplasm. The nuclei showed hyperchromasia, irregular borders, and large nucleoli. A few pyknotic forms were found. Anisokaryosis, perinuclear vacuolization, and multinucleation were prominent features. The cytoplasm varied from orange to green by the Papanicolaou stain. A few cells had vacuolated cytoplasm. This vacuolization was interpreted (incorrectly) as a degenerative change. No clusters of malignant cells were present.

Diagnosis: Positive for malignant cells. Compatible with squamous-cell carcinoma in situ.

Pleural Fluid (Fig. 3).—Sections prepared from paraffin cell blocks and stained with hematoxylin-phloxine disclosed almost solid masses of tumor cells enmeshed in fibrin. These cells were similar to those found in the vaginal fluid except for more cytoplasmic vacuolization and a propensity to form clusters or rosettes. Smears of the sediment stained according to the technique of Papanicolaou contained similar cells.

Diagnosis: Positive for malignant cells, probably adenocarcinoma. Primary site most likely ovary but gastrointestinal and biliary tracts also possible sites.

Peritoneal Fluid (Fig. 4).—Smears prepared from the sediment were essentially similar to those of the pleural fluid. Degenerative forms were somewhat more numerous.

Pathological Examination

Surgical Specimen.—The left ovary was slightly enlarged and partially replaced by friable, grayish-white tissue which formed papillary surface projections. Scattered small papillary implants were present on the surface of the right ovary, fundus of the uterus, Fallopian tubes, and within a large mass of omental tissue.

Microscopic Examination: This disclosed a papillary adenocarcinoma with both well-formed glandular structures (Figs. 5 and 6) and medullary undifferentiated areas. Papillary formations were seen on the outer surface while masses of tumor deeply invaded the substance of the ovary. A few cells exhibited vacuolated cytoplasm with occasional signet-ring forms. Foci of necrosis and hemorrhage were present. The metastatic nodules were similar. Multiple sections of the Fallopian tubes, endometrium, and cervix failed to disclose any implants. No malignant cells were found within the lumina or lymphatics of these structures.

Autopsy: The peritoneum and pleurae were found to be studded with tumor implants. Metastases were found in the iliac, hypogastric, and periaortic lymph nodes and within the lumina of rami of the pulmonary artery.

Comment

The cytological features of the vaginal fluid were initially interpreted as representing superficial and parabasal dyskaryosis indicative of epidermoid carcinoma in situ.[5] The absence of the clusters or rosettes characteristic of uterine adenocarcinoma is worthy of note. Wachtel and Plester[4] found this to be helpful in differentiating ovarian tumor cells from those of uterine adenocarcinoma. In retrospect, the presence of the vacuolated cells, which were incorrectly interpreted as degenerating cells, should have aroused our suspicions. Another finding which should have received serious consideration was the sudden disappearance of all atypical cells in subsequent vaginal smears, especially in view of their abundance in the original ones. We have never encountered such an occurrence with cervical neoplasms unless they were complicated by severe secondary infection or cervical stenosis distal to the lesion. Repeated pelvic examinations disclosed no enlargement of the ovaries and the patient had no gynecological complaints. The former became understandable when, at surgery, the ovary was found to be minimally enlarged despite its extensive replacement by neoplasm. It was only after neoplastic periovarian adhesions had formed that a suspicious mass could be palpated.

The development of pleural effusion and its cytologic findings first directed attention toward the ovaries. The malignant cells in the pleural fluid were essentially similar to those in the vaginal smears except for the additional features of cluster formation and cytoplasmic vacuolization. It was now apparent that we were dealing with a pleomorphic adenocarcinoma which had exfoliated cells into both vaginal and pleural fluids. Despite the absence of palpable masses, an ovarian cancer with pleural metastases seemed the most likely possibility, as proved to be the case.

Histologically, this tumor was a papillary adenocarcinoma with medullary, undifferentiated components. Seven of eight previously reported ovarian tumors with positive vaginal smears were also adenocarcinomas,[1-4] the other was a malignant teratoma.[3] Clinical and pathological details were presented in only two of these eight cases.[1, 2] Both of these patients had gynecological symptoms. One had a palpable adnexal mass.[2] In the other, the failure to palpate a large tumor was attributed to her marked obesity. In both instances there was severe involvement of the Fallopian tube.

We believe that this is the first report of the finding of malignant cells in the vaginal smears of a patient with an ovarian carcinoma, prior to the development of symptoms or signs referable to that tumor and without tumor implants within the Fallopian tubes or endometrium. The only explanation for the presence of malignant cells in the vaginal secretion in our patient is that they exfoliated from the surface of the ovary and were carried through the tube into the cavity of the uterus. The subsequent absence of such cells in the vaginal secretion suggests that this occurs in intermittent "showers" rather than continuously.

Summary

1. A papillary adenocarcinoma of the ovary is reported, with malignant cells in the vaginal smear of an asymptomatic woman who had no palpable tumor and who was found to have no endometrial or endosalpingeal metastases.

2. Ovarian adenocarcinoma may be suspected when vaginal smears disclose malignant cells which are not typical of cervical or endometrial tumors, especially when the individual cells suggest adenocarcinoma but without formation of clusters or rosettes. Intermittent appearance of "showers" of such cells in vaginal smears may be characteristic of ovarian carcinoma.

The photomicrographs were prepared by Mr. Mort Russin.

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INTRAUTERINE FOREIGN BODY AND PREGNANCY

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FOREIGN bodies in the uterus, although rarely found, are usually introduced either to cause interruption of a pregnancy or to prevent a pregnancy. Their rarity in the past was noted by Alfred Poulet[1] in his book published in 1880. In his chapter on foreign bodies in the uterus, he cited seven cases, varying from a twig of a tree to a piece of a rubber catheter in the uterus. From his review of the literature at that time he was able to find only one death due to an intrauterine foreign body. Heineck[2] in 1913 operated on several patients because of a "self-retaining uterine tube" which was to prevent conception. Lazarus[3] in 1925 removed a piece of a "wishbone type" of pessary which had been broken off by a midwife in an attempt at removal after it had been worn for several months to prevent conception.

Complications such as the perforation of the uterus by a foreign body can occur. One patient inserted a pencil into the uterus to stop uterine bleeding which had occurred after a 57 day period of amenorrhea. The patient was operated on and the pencil was found lying parallel to the vertebral column. The small hole in the uterus was sealed off by omentum and no sutures were required to close the defect.[4] Sussex[5] reported the penetration of a gold stem pessary through the uterine wall and subsequent subtotal hysterectomy. Leynen[6] reported the perforation of a gravid uterus by a shell fragment. The patient recovered, but the outcome of the infant was not clearly stated.

More severe complications can arise even though the uterus is not perforated, as noted by Israel and Harrel[7] in their paper. One of their patients developed severe endocervicitis within eight weeks after insertion of a wishbone pessary; a second had acute parametritis; and the third was critically ill with generalized peritonitis.

Occasionally the end result is more favorable. In a case reported by Brawner,[8] which is different from those previously cited in that the foreign body was not intentionally introduced, a needle was broken off and lost in the uterine wall during an emergency operation. Forty-five days later the patient passed the remaining part of the needle per vaginam without complications.

At the present time, x-ray of the pelvis is helpful in detecting foreign bodies, particularly if of glass, metal, or rubber. X-ray was first used on a patient who had inserted a crochet needle into the uterus because she was pregnant. The needle had a metal cap on the end of it and when the needle was withdrawn the cap remained in utero as was seen on the skiagram. The patient later aborted both the needle and the fetus.[9]

Although in recent times the intrauterine foreign bodies are usually pieces of the wishbone type of pessary that have been broken off during careless removal by the patient or a charlatan, other devices are still occasionally used. Cashwell[10] in 1942 presented the case of a patient who had introduced a bobby pin into the uterus to "open up the cervix" because her menstrual period had been overdue two weeks. The bobby pin was "lost" in the process. A hysterotomy was performed later and a dead fetus of approximately four months' gestation and the untarnished bobby pin were removed, the latter being found between the placenta and the anterior uterine wall. Nuñez[11] attended a patient in prolonged labor, the cause of which was found to be an intrauterine wooden spool which was interfering with the descent of the head. The spool was removed and, after delivering an apparently viable infant, the patient recovered.

Various types of intracervical and intrauterine devices are available on the market today. They are not without danger, however, not only because of possible tissue injury,

but also because of the possibility of an ascending infection from the vagina into the uterus.[12] They act as an irritant, causing profuse discharge, uterine contractions, abortion, metritis, peritonitis if the uterine wall is penetrated, and may cause the death of both the fetus and the mother.

Case Report.—A 27-year-old white woman, para iii, was first seen on Jan. 9, 1952, with the chief complaint of amenorrhea. Her periods had been regular until her last normal menstrual period which occurred on Sept. 7, 1951. She did not think she could be pregnant because she had had a gold wedding ring placed in the cervix in August, 1949, by a chiropractor as a contraceptive measure following the delivery of her last child on June 13 of that year. The ring was removed, cleaned, and reinserted in August, 1950.

On physical examination the patient was a well-developed, well-nourished white woman appearing neither acutely nor chronically ill. On examination of the abdomen, a mass two fingerbreadths above the symphysis was palpated. No fetal heart sounds were heard and no movement was noted. The uterus was symmetrically enlarged to the size of a four months' pregnancy. There was no evidence of a ring in the cervix or vagina. The cervix presented a transverse os but otherwise was not remarkable.

The impression was: (1) uterine pregnancy with expected date of confinement about June 13, 1952, and (2) foreign body in the uterus (from the history).

A flat plate of the abdomen was taken and the report was that there was a small fetal outline which was thought to represent a pregnancy of approximately 14 to 16 weeks visualized to the right of the sacrococcygeal segment. Above this level, at the level of the lower midsacrum, was a rounded ring of metallic density which measured about 2 cm. by 1½ cm. (Fig. 1).

The patient was seen at rather frequent intervals thereafter in an effort to detect any signs of a threatening abortion.

On April 1, a flat plate of the abdomen was taken which disclosed the metallic ring to be at the level of the lower coccyx, slightly to the right. There was a single fetal outline visualized, breech presentation (left sacroanterior), and from the fetal development it was thought that the pregnancy had advanced to 28 to 30 weeks (Fig. 2).

On May 10, the cervical dilatation was 2 cm. Two weeks later it was 4 cm., the fetus being in a right sacroanterior position at minus 1 station.

During the following weeks the fetus rotated, and on May 31 a third set of plates, flat and oblique, was taken. These suggested that the pregnancy had advanced to approximately 38 weeks. However, the previously described ring noted at the level of the coccyx could no longer be identified (Fig. 3).

On June 14, the cervix was dilated to 5 cm., was completely effaced, and "ripe." The patient went into spontaneous labor on June 17 and delivered a viable full-term male infant. The placenta was intact, and showed some scattered areas of fibrosis. The postpartum course was entirely uneventful.

Six weeks post partum neither the mother nor the infant were having any difficulties. They have both been seen several times since and both were doing quite satisfactorily.

Comment

This case is presented because it is rather unusual for a patient to have a foreign body in the uterus for two years and eight months without symptoms, as well as becoming pregnant in spite of the foreign body and proceeding to term. She presented no symptoms of endometritis or even increased discharge, and at no time during the antepartum course did she run an elevated temperature or threaten to abort.

The few cases that have been found in the literature in which a foreign body was introduced either before or following conception have practically all had one common result, namely, the expulsion of a nonviable fetus before term.

If an attempt had been made during the antenatal course to remove the ring, the end results would certainly have been fatal for the fetus and probably would have caused complications for the mother. Since the patient did abort the ring, it obviously was lying

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Anteroposterior roentgenogram showing a small fetal outline to the right of the sacrococcygeal segment, approximately 14 to 16 weeks in development. (Lines point to fetal bones.) Above this, at the level of the lower midsacrum, is the intrauterine ring which was inserted in the uterus as a contraceptive device.

Fig. 2.—Anteroposterior view showing a single fetal outline, breech presentation, 28 to 30 weeks in development and the metallic ring at the level of the lower coccyx, slightly to the right of the midline. The ring has descended to a lower level than is noted in Fig. 1.

Fig. 3.—Anteroposterior view showing a single fetus of approximately 38 weeks' development. The metallic ring noted in Figs. 1 and 2 can no longer be seen, the patient apparently having passed the ring per vaginam during the course of cervical dilatation in the latter weeks of pregnancy.

between the uterine wall and membranes and free of the placental area, otherwise it would have remained until, or possibly after, delivery.

We must express regret that we could not salvage the foreign body, but during the last trimester when the fetus was rotating in its position from a breech to a cephalic presentation, when the cervix was dilating and becoming effaced, and perhaps because of the weight of the ring itself, it apparently was passed per vaginam, unnoticed by the patient, and lost.

Summary

1. A case is presented in which a patient had a foreign body (gold wedding ring) in the cervix for a year as a contraceptive device, had it removed, cleansed, reinserted, and then became pregnant. She passed the ring in the last trimester and then delivered a full-term viable infant and had a normal puerperium without complications.

2. An intrauterine foreign body was present for two years and eight months and caused no symptoms.

3. This case is presented because so very few of this nature have been reported, and we believe this to be the first in American literature.

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GRAVES-GILBERT CLINIC
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DIAPHRAGMATIC HERNIA COMPLICATING PREGNANCY

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A DIAPHRAGMATIC hernia that complicates pregnancy is a rarity. Only 11 cases[1-9] of this type have been reported since 1916.

Diaphragmatic hernia of the esophageal hiatus type is not uncommon during pregnancy according to Rigler and Eneboe.[10] This type of hernia apparently is seldom significant as a complicating factor.

The etiology of these hernias is frequently not determined. Trauma and the repeatedly elevated intra-abdominal pressures that occur as a result of multiparity[11] are factors.

Most frequently noted as a symptom is epigastric pain or burning sensation. Nausea, vomiting, heartburn, salivation, and dyspnea are usually present. These may all be aggravated by ingestion of food or fluids. The horizontal position has frequently been found to aggravate these symptoms. Another symptom of significance is anemia. Diagnosis is made on physical examination and x-ray. Physical findings are those of any unilateral space-taking lesion plus the presence of adventitious sounds over the side involved.

Roentgen examination of the chest is the one most important diagnostic aid. Barium meal and fluoroscopy plus the Trendelenburg position may be necessary to demonstrate the lesion.

If a herniation of this type complicates pregnancy the mortality is extremely high. The diagnosis has rarely been made before symptoms of obstruction or strangulation develop. Six of the 11 cases noted previously were fatal. The patient in the present case also died. The entire series of 7 fetal cases out of 12 gives a mortality figure of 58.3 per cent.

Treatment is symptomatic if surgical repair is not attempted.

Below is presented a case of this type:

Mrs. I. W. (LAFB Hospital, 52-161-1), a white 25-year-old gravida v, para iv, was well during the first three and one-half months of her present pregnancy. She was Rh positive and had a negative Wassermann test. Conception occurred about Jan. 26, 1952, and the expected date of confinement was Oct. 19, 1952.

Her four previous pregnancies were completely uncomplicated, the last in 1949. Past history was uneventful except for an automobile accident in November, 1951. At that time she was unconscious four days due to cerebral concussion. The left superior and inferior pubic rami and several ribs were fractured.

At the beginning of the fourth month of her present pregnancy she noticed severe headache, chills, fever, and occasional vomiting. She had received no previous prenatal care and was hospitalized at a neighboring Air Force Base on May 12, 1952.

On admission the above-mentioned symptoms were present. Physical examination revealed a fairly well-developed but thin, dehydrated, white woman who was in obvious distress due to a severe headache. Blood pressure, pulse, and temperature were normal. Examination revealed normal findings except for upper midabdominal tenderness. The uterus was enlarged to just below the level of the umbilicus.

Laboratory studies were completely within normal limits. These included normal complete blood count plus urinalysis. Routine chest x-ray taken May 13, 1952, was normal.

It was believed at this time that the primary complaint was a tension headache. The patient improved with phenobarbital sedation and intravenous fluids. On May 15, 1952, she was believed to be sufficiently improved and she was discharged from the hospital.

The patient was readmitted on May 16, 1952. At this time she again appeared acutely ill. Tenderness and pain had developed in both costovertebral angles plus a temperature elevation to 103° F. Diagnosis of acute pyelonephritis of pregnancy was made after urinalysis revealed 15 to 20 pus cells per high-power field. Urine culture was not reported.

Treatment consisted of daily intravenous fluids in 1,000 to 2,000 c.c. amounts plus streptomycin, 2.0 Gm., procaine penicillin, 600,000 units, and Gantrisin, 0.5 Gm., four times daily. On May 18, 1952, after three days of therapy and no apparent improvement, the penicillin dosage was doubled. Response continued to be slow and the patient became afebrile after 6 days of therapy. Urine examination on May 21, 1952, revealed 20 to 30 pus cells per high-power field and a trace of albumin. Repeat complete blood count on May 21, 1952, revealed a drop in hemoglobin level from the original 11.05 Gm. reading to 8.75 Gm. Red blood count had similarly dropped from 3.76 million cells to 3 million. A 500 c.c. blood transfusion was given on May 25, 1952, without reaction. On May 26, 1952, nausea and vomiting had become the prominent symptoms and she was transferred to our hospital for further evaluation and treatment.

On admission to Lackland Air Force Hospital the patient was obviously acutely ill. The general physical findings were as previously described. She was still quite dehydrated and left costovertebral angle tenderness was present. The uterus was enlarged to just below the umbilicus. The patient had lost 12 pounds since onset of present illness, her normal weight being 122 pounds.

Laboratory studies revealed red blood count 3.36 million, hemoglobin 10.5 Gm., white blood count 10,950, and differential count as follows: neutrophils 4-86, lymphocytes 9, monocytes 1. Bleeding and coagulation time were 2 minutes, 15 seconds, and 2 minutes, 30 seconds, respectively. Urinalysis revealed a large number of bacteria and pus cells too numerous to count. Occult blood in the urine was plus 4. Complete blood chemistry determination including serum potassium, sodium, and carbon dioxide combining power were normal. The nonprotein nitrogen was elevated to 45 mg. per cent and chlorides were over 580 mg. per cent. Prothrombin time and van den Bergh tests were normal. It was believed that the elevation of serum chlorides was due to infusions previously received and this ion was reduced in fluids administered. Urine culture was positive for *E. coli* and the patient responded well to intravenous terramycin therapy (500 mg. every 6 hours) and fluids. A hyperemesis diet plus sedation controlled the vomiting satisfactorily.

Chest x-ray taken on May 30, 1952, revealed an air-fluid level to be present in the left side of the chest at the level of the fourth to fifth ribs. In view of the decrease in vomiting the patient was transferred to the medical service for further study of chest findings.

While on the medical service re-x-ray of the chest showed marked elevation of the left hemidiaphragm to the second anterior interspace with associated displacement of the stomach. Fluoroscopy with barium swallow showed the stomach and possibly the colon to be herniated into the left thoracic cavity.

The patient was then transferred to Randolph Air Force Hospital where the chest surgery is done in this area. She was sent for repair of the diaphragmatic hernia.

The patient remained at Randolph Air Force Hospital one week during which time she received routine study preparatory to surgery.

On June 8, 1952, the membranes supposedly ruptured and she had some vaginal bleeding. Uterine contractions developed at 5 minute intervals. In view of the onset of possible late abortion she was returned to the obstetrical service at Lackland on June 9, 1952. Labor, however, failed to ensue and a re-evaluation of the patient's status was made. The chest surgeons advised emptying the uterus before proceeding with repair of the hernia.

It was decided after lengthy consultation to carry this patient under close observation until a viable infant was obtained. From then on the patient was placed on the following regime of therapy:

She received six small feedings daily of bland high-calorie, high-protein food. Protein supplement was given in a milk shake between feedings. An antispasmodic such as tincture

of belladonna was given as indicated for vomiting. The hemoglobin was maintained at the 11 Gm. level by an additional 750 c.c. of blood. The patient was kept as inactive as possible and elevated in bed when sleeping.

Repeated chest x-ray on June 30, 1952, revealed all the herniated viscera to have returned to the abdomen and the left lung to have completely re-expanded. A pleuritic reaction at the base of the left lung was believed helpful in preventing recurrence of herniation.

This patient from the time of readmission until July 26 was relatively asymptomatic. She gained 6 pounds under the above-mentioned treatment.

During mid-July severe domestic difficulties developed. Due to this, arrangements were made to have the patient transferred to a civilian hospital in her home town.

This was never accomplished. On July 27, 1952, a severe bout of vomiting occurred. Sedation, intubation with constant suction, and intravenous fluids were required to control the vomiting. X-ray at this time revealed herniated viscera to be present and they filled 80 per cent of the left chest cavity.

On July 28, 1952, after 4,500 c.c. of gastric contents were removed by suction, the patient began to retain food and the course remained uneventful until August 3.

At this time a recurrence of severe vomiting developed. Similar procedures were attempted that had been successful on July 27; however, the patient refused to leave the Levine tube in place. The patient was seen in consultation by the chest surgeons and although her condition was critical it was believed that intestinal obstruction was not present. No improvement occurred August 4 and at 6 P.M. it was decided to attempt induction of premature labor by cervical and vaginal packing.

The patient was taken to the delivery room and before she was placed on the delivery table for induction of labor she was suddenly unable to breathe and died. Attempts at resuscitation were unsuccessful.

Postmortem examination revealed as prominent findings: (1) herniation of the middle and upper portions of the stomach plus the mid-portion of the transverse colon through a defect in the diaphragm; (2) dilatation of the stomach within the left thoracic cavity; (3) rupture of the stomach (estimated 900 c.c. of gastric contents and air in the left pleural cavity); (4) petechiae and ecchymosis of the mucosa of the stomach, duodenum, jejunum, ileum, ascending, transverse, and descending colons; (5) chronic pyelonephritis, bilateral, slight; (6) male fetus of 1,150 grams and estimated at 7 months' gestation; (7) defect in the left leaflet of the diaphragm, 6 cm. in diameter, 2 cm. lateral to the esophageal hiatus.

Summary

A diaphragmatic hernia that complicates pregnancy is rare in spite of the high incidence of esophageal hiatus hernias reported. Only 11 cases were found in the literature from 1916 until today. Trauma and multiparity are important etiological factors. Diagnosis is usually confirmed by x-ray examination. The Trendelenburg position is often helpful in demonstrating the lesion. Mortality is high due to failure to diagnose this condition before symptoms of obstruction or strangulation develop. The over-all mortality is 58.3 per cent. If repair of the hernia is not attempted treatment is symptomatic.

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MULTIPLE MALIGNANT TUMORS OF THE UTERUS*

Report of a Case

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THE occurrence of multiple primary malignant tumors is rare. The following case is presented as an unusual example of three simultaneous malignant tumors occurring in a single organ.

This is the case of a 52-year-old white nullipara who developed postmenopausal bleeding in August, 1951. She first visited a physician in October, 1951, and pelvic examination disclosed a somewhat enlarged uterus with a definite mass on the posterior surface. The cervix appeared smooth. The patient refused surgery, but continued to bleed so freely that she returned one month later. At this time total hysterectomy with bilateral salpingo-oophorectomy was done. This was followed by intensive pelvic x-irradiation. Early in January of 1952, metastatic disease of the fourth thoracic vertebra was noted on roentgen examination, and a metastatic nodule on the anterior vaginal wall was found on pelvic examination. Up until this time the patient had been symptom free, but now developed dyspnea which became progressively more severe until the time of her death in February, 1952, six months after the onset of symptoms and three months following surgery.

The resected uterus was found to contain three distinct and unrelated primary malignant lesions. In the cervix there was squamous carcinoma of a highly anaplastic nature invading deep into the stroma (Fig. 1). The endometrium for the most part was replaced by closely packed, fairly well-differentiated acini of adenocarcinoma (Fig. 2). In one section of the myometrium there was a well-defined leiomyosarcoma (Fig. 3).

Needle biopsy of the fourth thoracic vertebra, done to direct therapy, was histologically similar to the cervical primary tumor. Biopsy of the nodule in the vaginal wall also conformed to the appearance of squamous carcinoma.

At postmortem examination metastatic cancer was found to be present in the pelvic fascia, periaortic and mediastinal lymph nodes, kidneys, liver, and lungs. Ninety to 95 per cent of the pulmonary tissue was replaced by metastatic tumor (Fig. 4). In every instance of the many portions of metastatic tissue examined, squamous carcinoma was the only type found. Examples of metastases from the lungs (Fig. 5) bear a marked resemblance to the primary cervical tumor and some areas contain giant, bizarre nuclei which are not unusual in metastases of squamous carcinoma of the cervix. Not a single metastasis of adenocarcinoma or of leiomyosarcoma was found.

The simultaneous occurrence of three distinct malignant tumor types in the uterus is somewhat of a medical curiosity. The presence of widespread metastases from the squamous carcinoma alone is not so curious, since adenocarcinoma of the endometrium or leiomyosarcoma of the myometrium occurring alone are likely to metastasize later and less widely.

The general question of multiple malignant neoplasms is an important clinical problem that arises on making the diagnosis of cancer in any patient. Analysis of previous statistical surveys of this problem has suggested that certain individuals are predisposed to multiple neoplasms or that multiple cancers occur more frequently than would be expected by chance alone.[1] However, a recent statistical survey by Mider and

*Read at a meeting of the Obstetrical Society of Philadelphia, March 5, 1953.

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associates[2] offers new opposition to this assumption. Records of 4,000 patients with primary malignant neoplasms of stomach, uterus, breast, large intestine, or hematopoietic system were studied. Four and five-tenths per cent of these had one or more other primary cancers. By comparison with a population group of the same age and sex, this is significantly more than would be expected to occur by chance alone. However, as the

Fig. 1.

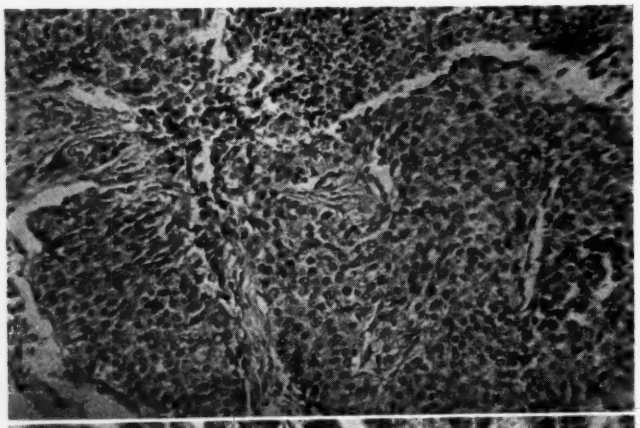

Fig. 2.

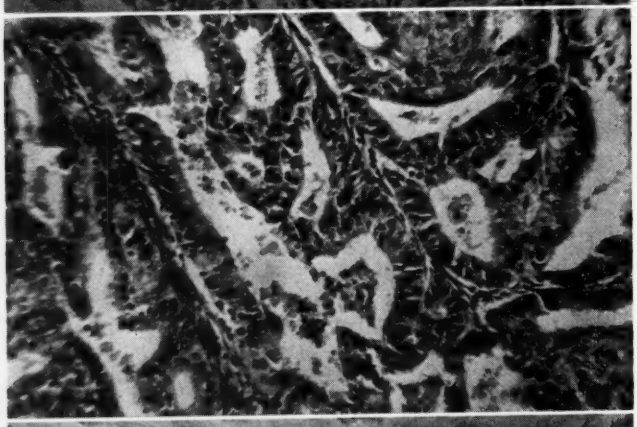

Fig. 3.

Fig. 1.—Histological section of anaplastic squamous carcinoma of cervix. (×400.)

Fig. 2.—Section of densely packed acini of adenocarcinoma of uterine fundus; note paucity of stroma. (×400.)

Fig. 3.—Large, hyperchromatic, spindle-shaped nuclei are typical of leiomyosarcoma. (×400.)

multiplicity fell into tumors primary in the breast and colon there is good indication that this figure is due to the over-all high incidence of multiple cancers in these two sites, and not to a true tendency to multiple primary sites of cancers elsewhere. On the basis of the study cited, it would seem that multiple malignant tumors of the uterus are probably due to chance alone and would occur rarely.

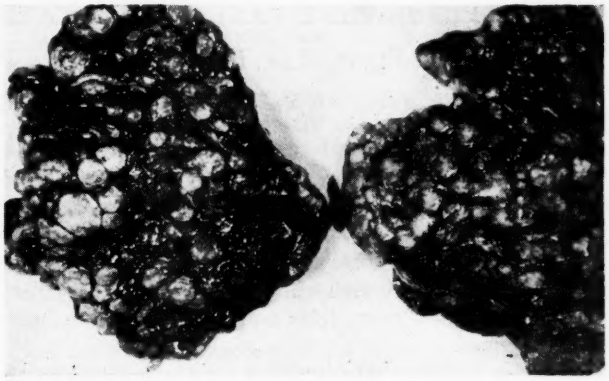

Fig. 4.—Lungs removed at postmortem examination are 90 to 95 per cent replaced by metastatic tumor nodules.

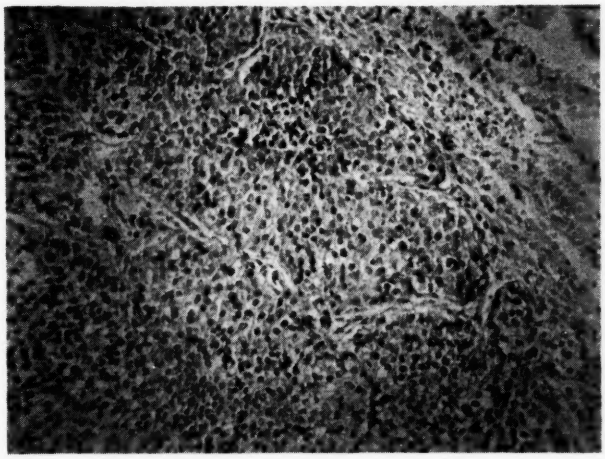

Fig. 5.—Histological section of metastasis of poorly differentiated squamous carcinoma of the cervix found in the lungs. (×400.)

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CONGENITAL, HEREDITARY, DIFFUSE NONTOXIC GOITER AS A CAUSE OF PERSISTENT FACE PRESENTATION

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TUMORS of the fetal neck, especially enlargements of the thyroid gland, invariably are mentioned in publications concerning the etiology of face presentation. However, while 609 cases of face presentation are reported in the recent literature,[1-8] only one case[2] reported is attributed to a tumor of the neck of the fetus. This tumor was a cystic hygroma that prevented flexion of the fetal head. The mother was delivered of a stillborn infant by internal podalic version followed by breech extraction.

The following case report also exemplifies marked interference in flexion of the fetal head caused by a thyroid tumor.

Mrs. N. C. (OMH No. 8221), a 36-year-old para iii, gravida iv, was estimated from menstrual history to be at term on March 31, 1952. The fetal membranes ruptured spontaneously at 10:40 A.M. on that date, and the patient was admitted to the Oneida Maternity Hospital 12 hours later. Occasional mild contractions had ensued. The patient's prenatal course had been uneventful. The pelvis was typed as gynecoid. A large, diffuse nontoxic goiter of many years' standing had been treated with Lugol's solution in the last trimester of pregnancy. Past history revealed three deliveries at term by a midwife. All three of these infants are alive and well, but their birth weights are not known.

The general physical findings on admission were unremarkable, except for the large goiter and moderate obesity. The patient's temperature was 97.8° F.; blood pressure was 130/70. The red blood count was 4.9 million and the hemoglobin 14.5 Gm., blood type O, Rh positive. Urinalysis for sugar and albumin was negative. The fundus was 30 cm. above the symphysis; the fetal back was directed to the right, and the fetal heart tones were heard best in the left lower quadrant at the rate of 144 per minute. Mild uterine contractions occurred at 10 to 15 minute intervals, and were of 25 to 30 seconds' duration. Sterile vaginal examination revealed the cervix effaced, soft, and two fingerbreadths dilated. Amniotic fluid escaped freely. The fetus was in cephalic presentation in the left mentum transverse position at station minus four.

After 9 hours of observation, during which time the uterine contractions remained ineffectual and the cervix unchanged, the patient was given Calgluquine, 5 c.c. intravenously and 5 c.c. intramuscularly. This drug failed to stimulate labor. Prophylactic penicillin therapy was begun at this time.

The patient continued to have painful, ineffectual uterine contractions throughout the day. Approximately 17 hours after admission, the diagnosis of primary uterine inertia with premature rupture of the fetal membranes and face presentation was firmly established; and the patient was treated with intravenous fluids and morphine sedation.

After she had rested for approximately 14 hours, at 6:30 A.M. on April 2, 1952, stimulation of labor was again attempted, this time with castor oil and a hot enema. Again, labor did not ensue. It was considered inadvisable to use Pitocin at this point because of the malpresentation and multiparity. Also, in view of the existence of a "ripe" cervix and ruptured membranes, it seemed reasonable to assume that minimal stimulation would establish labor. The patient had remained afebrile and the fetal heart tones were good.

At 10:30 A.M. a No. 5 Voorhees bag was inserted and ½ pound continuous traction applied. After 5 hours and 15 minutes, uterine contractions occurred at intervals of 13 to 15 minutes and were of 25 to 30 seconds' duration. The cervix remained unchanged.

Since the methods employed had failed to stimulate labor, the bag was left in place with traction, and ½ minim of Pitocin was administered subcutaneously at 3:45 P.M. on April 2, 1952. Excellent uterine contractions occurred at 2 minute intervals and were of 50 seconds' duration. After 1 hour and 25 minutes, the Voorhees bag was expelled into the vagina. Examination under ether anesthesia revealed the cervix completely dilated and the position left mentum transverse at minus four station. Thorn's maneuver was unsuccessful. An internal podalic version was accomplished with considerable difficulty, and a 2,940 gram female infant was delivered by breech extraction. The third stage of labor lasted 8 mintues; blood loss was estimated at 150 c.c.

The infant was in poor condition (asphyxia pallida), but responded to endotracheal catheterization and oxygen therapy. Examination of the infant disclosed a large, diffuse goiter of the same relative size as that of the maternal goiter.

During the neonatal period, it was impossible to flex the infant's head so that the chin would lie on the upper chest, because of the enlargement of the thyroid gland. Thus, the etiology of the face presentation in this case is evident.

One drop of Lugol's solution was added to the infant's daily formula. At six weeks of age the infant's thyroid exhibited only minimal enlargement and the chin could easily be flexed to the chest.

The puerpera had an uncomplicated, afebrile recovery and was discharged on the fifth postpartum day. Examination at 6 weeks post partum revealed the mother's goiter to be unchanged in size; the genitourinary findings were compatible with the patient's multiparity.

Comment

There is general agreement that a moderate degree of hypertrophy of the thyroid is a physiologic process occurring in the course of normal pregnancy. Also agreed upon generally is the particular importance of a sufficient supply of iodine for the pregnant woman in order to prevent cretinism in her offspring. There is, however, no agreement concerning the role of diffuse nontoxic (simple colloid) goiter during pregnancy. Eastman[9] states that simple colloid goiter, if not attended by hypothyroidism, probably has no influence on pregnancy, or vice versa. MacBryde[10] notes definite hereditary tendencies in the transmission of simple goiter, frequently with an associated cretinism in the offspring. He remarks further that, with few exceptions, iodine will prevent the myxedema which is occasionally seen in this type of goiter. Of more importance is the fact that the drug will rarely fail to prevent thyroid enlargement in the child of a pregnant woman with goiter. Litzenburg and Carey[11] have reported excellent results with the use of thyroid extract during pregnancy in the therapy of hypothyroidism, whether associated with diffuse nontoxic goiter or not.

Certainly, active prophylactic therapy is obligatory for the pregnant woman with goiter, as an attempt to prevent hereditary and/or congenital diffuse nontoxic goiter, possible cretinism, and the perils of persistent face presentation.

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611 Heyburn Building.

Items

American Board of Obstetrics and Gynecology

The general oral and pathology examinations (Part II) were conducted at the Edgewater Beach Hotel, Sunday, May 17, through May 24, 1953, at which time 315 candidates were certified.

The next scheduled examination (Part I), written examination for all candidates, will be held in various cities of the United States and Canada on Friday, Feb. 5, 1954. Candidates are urged to make application as soon as possible.

All candidates for admission to the examinations for certification by the Board are required to submit with their application a plain typewritten list of all patients admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application, with the diagnosis, pathological diagnosis, nature of treatment, and end result.

Twenty-five Case Abstracts are due immediately after notification of eligibility and are to be sent by the candidate to the Secretary.

Attention of all candidates is called to a change in date. Application for examination or re-examination, as well as requests for resubmission of case reports, must be made to the Secretary prior to Oct. 1, 1953.

Requests for application forms for Appraisal of Incomplete Training, for Certification, current Board Bulletins, and Preceptorship or Supplemental Training Forms should be accompanied by a large stamped, self-addressed envelope and mailed to:

ROBERT L. FAULKNER, M.D., Secretary
American Board of Obstetrics and Gynecology
2105 Adelbert Road
Cleveland 6, Ohio

The following candidates were certified by the American Board of Obstetrics and Gynecology, May 24, 1953, at the Edgewater Beach Hotel, Chicago, Ill.

Abrams, Raymond H.	2618 Oak Lawn	Dallas, Texas
Abrams, Walter	3 Plaza Park	Forest, Ill.
Adler, Daniel H.	1269 President St.	Brooklyn 13, N. Y.
Arje, Sidney L.	U. S. Naval Hospital	St. Albans 25, N. Y.
Baggs, Wilbur J., Jr.	91 29th St.	Newport News, Va.
Balz, Fredric F.	Medical Dental Bldg.	Olympia, Wash.
Bates, Charles R., Jr.	1518 10th St.	Wichita Falls, Texas
Beauchamp, Maurice Flavian	59 Trumbull St.	New Haven, Conn.
Bills, Ervine S.	Family Hospital, Naval Air Station	San Diego, Calif.
Birtch, Paul K.	216 Summer Street	Buffalo 22, N. Y.
Bjork, Floyd J.	15105 West Seven Mile Rd.	Detroit 35, Mich.
Blanchet, David	3500 East 17th Ave.	Denver 6, Colo.
Bodine, Charles D.	1220 North Walker	Oklahoma City 3, Okla.
Bookstaver, Paul Irwin	241 Cedar Lane	Teaneck, N. J.
Boros, Harold H.	405 North Bedford Dr.	Beverly Hills, Calif.
Brandman, Leonard J.	144 07 Sanford Ave.	Flushing, Long Island, N. Y.
Brantley, Julian C., Jr.	401 Falls Road	Rocky Mount, N. C.

Brantley, Julian T.	1018 North Elm St.	Greensboro, N. C.
Brennan, Robert J.	11 Muzzy St.	Lexington, Mass.
Brew, James D., Jr.	U. S. Naval Hospital	Bremerton, Wash.
Brown, Robert S.	U. S. Naval Station	Orange, Texas
Bryan, Williams McIver, Jr.	1433 Gregg St.	Columbia 1, S. C.
Bryans, Charles I., Jr.	U. S. Army Hospital	Fort Bragg, N. C.
Buckner, Robert C.	329 East Armour Rd., North	Kansas City, Mo.
Buell, James I.	3875 Wilshire Blvd.	Los Angeles, Calif.
Bugelski, Thaddeus J.	1012 Humboldt Parkway	Buffalo 11, N. Y.
Bullard, Arch H.	1003 Medical Arts Bldg.	Chattanooga, Tenn.
Burkhart, Samuel Ellsworth	13237 Superior Ave., East	Cleveland 12, Ohio
Bush, William M.	Medical Arts Bldg., 230 North 5th St.	Reading, Pa.
Campbell, Robert M.	Stimson Bldg.	Seattle 1, Wash.
Capraro, Vincent Joseph	277 Linwood Ave.	Buffalo 9, N. Y.
Caradine, Robert S., Jr.	1665 Madison Ave.	Memphis 4, Tenn.
Chapman, James C. F.	209 Main St.	Boise, Ida.
Chappell, Clifford C., Jr.	2434 Durant Ave.	Berkeley, Calif.
Chung, Joseph T.	720 North Michigan Ave.	Chicago 11, Ill.
Claiborne, Martin Duralde	1413 Delachaise St.	New Orleans 15, La.
Copeland, William E.	2127 Harwitch Rd.	Columbus 12, Ohio
Corcoran, Albert W., Jr.	1222 Brookline Blvd.	Pittsburgh 26, Pa.
Cornelison, Joe Lee	510 West Beauregard Ave.	San Angelo, Texas
Cotton, Walter Thomas	University Hospital, 42nd and Dewey Ave.	Omaha 5, Neb.
Coyle, John Jerome	1200 North Walker	Oklahoma City 3, Okla.
Crandall, Noble Franklin	209 East 6th St.	Jamestown, N. Y.
Crawford, Edward J., Jr.	1006 Highland Ave.	Shreveport, La.
Critchfield, Thomas W.	University of Kansas Medical Center	Kansas City, Kan.
Croce, Gene A.	195 Waterman St.	Providence 6, R. I.
Crowley, Edward X.	435 North Hillside	Wichita 8, Kansas
Culotta, Vincent A.	203 California County Bldg.	New Orleans, La.
Daly, Stephen L.	155 West Merrick Rd.	Freeport, N. Y.
Darling, Charles E.	673 Fisher Bldg.	Detroit 2, Mich.
Davis, Jack E.	1800 Wilson Ave.	Chicago 40, Ill.
Davis, James E.	133 South Lasky Drive	Beverly Hills, Calif.
Decker, David G.	Mayo Clinic	Rochester, Minn.
Dickson, Glenn S.	1505 Foulkrod St.	Philadelphia 24, Pa.
Dickson, William A.	511 North Main St.	Jamestown, N. Y.
Dignam, William J.	2626 33rd St.	Santa Monica, Calif.
DiLoreto, Panfilo C.	3919 John Road	Detroit 1, Mich.
DiPaula, Anthony Francis	11 East Chase St.	Baltimore 2, Md.
Doherty, John Henry	327 North Washington Ave.	Scranton, Pa.
Doolittle, Sidney B.	1504 State Tower Bldg.	Syracuse 2, N. Y.
Douglas, Robert H.	1209 Swann Ave.	Tampa 6, Fla.
Driscoll, John J.	511 Pleasant St.	Malden 48, Mass.
Drolett, Donald J.	609 North Washington Ave.	Lansing 15, Mich.
Dugan, Robert J.	11406 Euclid Ave.	Cleveland 6, Ohio
Duncan, William S.	3400 Forbes St.	Pittsburgh 13, Pa.
Dunlap, John C.	1806 Austin St.	Waco, Texas
Durham, William C.	317 Wallace Ave.	St. Matthews, Louisville, Ky.
Edmonston, George F., Jr.	208 Corbet St.	Tarentum, Pa.
Efstation, Thomas D.	34 West Market St.	Tiffin, Ohio
Egenolf, George F.	2290 6th Ave.	San Diego 1, Calif.
Ellett, Rufus P., Jr.	920 South Jefferson St.	Roanoke, Va.
Ellis, James W.	2122 West End Ave.	Nashville 5, Tenn.
Emich, John P., Jr.	3401 North Broad St.	Philadelphia 40, Pa.
Epperson, John W. W.	Henry Ford Hospital	Detroit, Mich.
Epstein, Isidore L.	215-02 Thirty-ninth Ave.	Bayside, N. Y.
Erwin, John Joseph	518 Medical Arts Bldg.	Baltimore 1, Md.
Evans, Tommy N.	1313 East Ann Street	Ann Arbor, Mich.
Fallon, Robert J.	1180 Beacon St.	Brookline, Mass.
Farley, Deane M.	6804 Windsor Ave.	Berwyn, Ill.
Feeny, Thomas M.	2279 Jackson Ave.	Ogden, Utah
Feldman, Harold J.	131 Linwood Ave.	Buffalo 9, N. Y.
Fening, Walter E.	201 South Main St.	Middletown, Ohio
Fettes, David S.	1051 East 7th St.	Brooklyn 30, N. Y.

Finch, Thomas V.	546 Golf St.	Sarasota, Fla.
Fischer, Richard H.	915 19th St., N. W.	Washington 6, D. C.
Fitzgerald, James Arnold	Watertown National Bank Bldg.	Watertown, N. Y.
Fitzsimmons, William R.	319 West Jefferson St.	Butler, Pa.
Flowers, Charles Ely, Jr.	University Memorial Hospital,	Chapel Hill, N. C.
Foley, Walter E., Jr.	201 West Second St.	Davenport, Iowa
Frank, Charles W.	1777 Grand Concourse	New York 53, N. Y.
Frantz, Alfred Strayer	Craft Press Bldg.	Chambersburg, Pa.
Friday, Walter C.	218 North Third St.	Burlington, Iowa
Friedman, Joseph M.	1730 Eye St., N. W.	Washington, D. C.
Gaiewski, Chester J.	414 South Oak Park Ave.	Oak Park, Ill.
Gallaher, Phyllis DeVit	1009 Park Place	Wilmington, Del.
Garber, Edgar Clyde, Jr.	1256 Fort Bragg Rd.	Fayetteville, N. C.
Gareis, Louis Calvin	1651 Northwick Court	Baltimore 18, Md.
	(Single certification in *Obstetrics* only)	
Geanuracos, George J.	932 East Main St.	Bridgeport 8, Conn.
George, Robert P.	159 South Main St.	Akron 8, Ohio
Getty, Ralph W.	National Bank Bldg.	Auburn, N. Y.
Giaccone, John S.	1990 McGraw Ave.	Bronx 62, N. Y.
Gibson, Ralph L.	U. S. Army Hospital	Camp Atterbury, Ind.
Gillam, John S.	807 Broadway	Fargo, N. D.
Goldberg, Oscar	1140 East 21st St.	Brooklyn, N. Y.
Goler, George G.	10300 Carnegie Ave.	Cleveland 6, Ohio
Goodrich, Frederick W., Jr.	326 State St.	New London, Conn.
Gordon, Lawrence E., Jr.	404 North Roan	Johnson City, Tenn.
Gottesfeld, M. Ray	4050 Montview Blvd.	Denver 7, Colo.
Gouldin, Robert P.	1930 Chestnut St.	Philadelphia 3, Pa.
Goyanes, Everardo	857 Carroll St.	Brooklyn, N. Y.
Gozan, Henry A.	118-01 224th St.	Cambria Heights 11, N. Y.
Graves, Robert S.	522 Walnut St.	Gadsden, Ala.
Green, Alan D.	104 South Michigan Ave.	Chicago 3, Ill.
	(Single certification in *Obstetrics* only)	
Griffin, Joe J.	602 West University Ave.	Urbana, Ill.
Grove, Pembroke Thomson	114 W. Boscawen St.	Winchester, W. Va.
Gulick, Charles R.	3720 Washington Blvd.	St. Louis 8, Mo.
Guthrie, Joseph A.	2580 Bancroft Way	Berkeley 4, Calif.
Hack, Rudolf W.	1095 D. Street	San Bernardino, Calif.
Hall, Lee A.	634 N. Grand Ave.	St. Louis 3, Mo.
Halter, Paul Edmund	2316 Valley Drive	Alexandria, Va.
Hammerschlag, Max L.	1777 Grand Concourse	Bronx 53, N. Y.
Hank, George C.	110 East Main St.	Madison, Wis.
Harden, Murray Eugene	716 Lafayette Life Bldg.	Lafayette, Ind.
Hardy, Julian P.	920 South 19th St.	Birmingham 5, Ala.
Harris, Bruce A., Jr.	174 Clinton St.	Brooklyn 2, N. Y.
Hartmann, William L.	Johns Hopkins Hospital	Baltimore 5, Md.
Hassett, Arthur Joseph, Jr.	232 Main St.	Brockton, Mass.
Hayden, Richard A.	Quarters Number Five	West Point, N. Y.
Hearin, Willard C., Jr.	108 Sykes Ave.	Portsmouth, Va.
Heery, Ralph D.	2367 Auburn Ave.	Cincinnati 19, Ohio
Hedgedus, William J.	2007 West 7th Ave.	Amarillo, Texas
Helman, Rowland J.	1010 Banks St.	Houston, Texas
Henderson, Hodgie C., Jr.	118 South Edgefield St.	Dallas, Texas
Hernquist, William C.		Austin, Pa.
Herron, James R., Jr.	1930 Chestnut St.	Philadelphia 3, Pa.
Hess, Leo	680 West End Ave.	New York 25, N. Y.
Hill, Edward R.	4231 Fulton Rd.	Cleveland 9, Ohio
Hoffman, David B.	31 Lincoln Park	Newark, N. J.
Hoffman, John Brooks	43 Maple Ave.	Greenwich, Conn.
Hopp, Frederick C.	Madigan Army Hospital	Tacoma, Wash.
Hulme, Harold B.	411 First National Bank Bldg.	Boise, Idaho
Hunt, William	Mayo Clinic	Rochester, Minn.
Hunter, Richard E.	50 Elm St.	Worcester 2, Mass.
Iandoli, Louis J.	90-07 169th St.	Jamaica, N. Y.
Ingenito, Gabriel A.	181 Edwards St.	New Haven, Conn.
Inglis, Robert M.	196 East State St.	Columbus 15, Ohio
	(Single certification in *Obstetrics* only)	

Ingram, James M., Jr.	1001 MacDill Ave.	Tampa 9, Fla.
Jackson, John Lenoir, III	1314 9th St.	Wichita Falls, Texas
James, Hal P.	128 South Bellevue	Memphis 4, Tenn.
Jesurun, Harold M.	Brooke Army Hospital	Ft. Sam Houston, Texas
Kaiser, Joseph E.	710 Wilshire Blvd.	Santa Monica, Calif.
Kay, Sidney A.	Gorgas Hospital	Ancon, Panama Canal Zone
Kerstein, Louis N.	333 Park Ave.	Rochester 7, N. Y.
	(Single certification in *Obstetrics* only)	
Keyes, John Lane	148 Barr St.	Lexington, Ky.
	(Single certification in *Obstetrics* only)	
Keys, Harry J.	1607 Neil Ave.	Columbus 1, Ohio
Kirk, John A.	331 Eugene Medical Center	Eugene, Ore.
Klein, Michael	10616 Euclid Ave.	Cleveland 6, Ohio
Knerr, Edgar D., Jr.	531 North Lime St.	Lancaster, Pa.
Knopf, Carl L.	530 Forrest Ave.	Drexel Hill, Pa.
Koerper, Victor E.	431 30th St.	Oakland 9, Calif.
Krezowski, Thomas K.	1154 Lowry Medical Arts Bldg.	St. Paul 2, Minn.
Krieger, James Stewart	38 10th Medical Group, Maxwell Air Force Base	Montgomery, Ala.
Krugman, Philip I.	727 West Peachtree St., N. E.	Atlanta 3, Ga.
Langley, Ivan I.	1020 Southwest Taylor	Portland 5, Ore.
Langston, Eugene Dent., Jr.	3015 West 85th St.	Inglewood 4, Calif.
LaSalvia, Lucy A.	1930 Chestnut St.	Philadelphia 3, Pa.
Lascelle, Philip	838 East 223 St.	New York 67, N. Y.
Lawrence, Arthur C.	210 East 32nd St.	Paterson 2, N. J.
Lea, Austin W.	1010 B St.	San Rafael, Calif.
Lee, James G., Jr.	Naval Air Station	Moffett Field, Calif.
Lee, James Harold, Jr.	U. S. Naval Hospital	Beaufort, S. C.
Lee, Stanley T.	750 Swift Ave.	Fresno, Calif.
Lenhert, A. Engle	2010 East 102nd St.	Cleveland 6, Ohio
Lewis, George C., Jr.	133 South 36th St.	Philadelphia 4, Pa.
Lewis, Norman	208 First National Bank Bldg.	Canton, Ohio
Lindstrom, William Carl	106 West 6th St.	Tulsa, Okla.
Lombardi, James Carl	1690 Milwaukee St.	Denver, Colo.
LoPresti, Carmelo E.	29 Washington Square West	New York 11, N. Y.
Luetke, William V.	1023 Regent St.	Madison, Wis.
Lunin, Arthur B.	2905 LaBranch St.	Houston 4, Texas
MacDonald, William James	221 Thayer St.	Providence 6, R. I.
MacNamara, William A.	Medical Arts Bldg.	Scranton, Pa.
Maher, Frank M.	104 South Michigan Ave.	Chicago 3, Ill.
Mahoney, Joseph P.	45-18 245th St.	Douglaston 62, N. Y.
Marsh, Memoir R.	441 Ocean Ave.	Brooklyn 26, N. Y.
Masterson, John G.	451 Clarkson Ave.	Brooklyn 3, N. Y.
Matthews, Charles S.	1296 Delaware Ave.	Buffalo 9, N. Y.
May, Thomas J.	88-03 Whitney Ave.	Elmhurst, N. Y.
McCartney, Charles Price	5841 S. Maryland Ave.	Chicago 37, Ill.
McCaskill, Melvin R.	1429 West 7th St.	Little Rock, Ark.
McConnell, Edward L.	2230 South Broad St.	Philadelphia, Pa.
McConnie, Randolph J.	Avenue de Diego 303	Santurce, Puerto Rico
McElin, Thomas W.	626 Church St.	Evanston, Ill.
McElrath, Percy J.	500 St. Marys St.	Raleigh, N. C.
McIntyre, Donald M.	325 9th Ave.	Seattle, Wash.
Meharg, John G.	311 Penn Ave.	West Reading, Pa.
Menold, William F.	317 Lowry Bldg.	St. Paul, Minn.
Meunier, Henry J.	1180 East 63rd St.	Chicago 37, Ill.
Mirick, Donald F.	226 Tucker Bldg.	Clinton, Iowa
Mitchell, Raymond W., Jr.	300 Long Ave.	Hamburg, N. Y.
Moss, Vassar Y., Jr.	121 University Place	Pittsburgh 13, Pa.
Muenzer, Robert Warren	1838 Parkwood Ave.	Toledo 2, Ohio
Nanzig, Reinard P.	1516 Wealthy	Grand Rapids 6, Mich.
Nelson, Dean F.	2404 Washington Blvd.	Ogden, Utah
Nereo, Oswaldo A.	36 Cedar St.	Taunton, Mass.
O'Donnell, Robert Porter	508 East South Temple	Salt Lake City 2, Utah
Oliver, Ernest B.	3217 Carlisle Rd.	Birmingham 9, Ala.
Olson, Lorin M.	5842 N. Kingsdale Ave.	Chicago 30, Ill.

Pallas, William C.	U. S. Naval Hospital,	Portsmouth, Va.
Palumbo, Leonard, Jr.	Duke Hospital	Durham, N. C.
Parker, Roy W.	104 20th Ave., North	Nashville, Tenn.
Parlee, Stephen	502 McLeod Bldg.	Edmonton, Alberta, Canada
Peck, Sidney Jan	5 Bernard St.	Great Neck, N. Y.
Penman, William R.	230 North Broad St.	Philadelphia 2, Pa.
Pennoyer, James	607 North Grand Ave.	St. Louis 3, Mo.
Persall, John Thomas, Jr.	302 S. F. C. Bldg.	Augusta, Ga.
Peters, William A., Jr.	206 South Road St.	Elizabeth City, N. C.
Piccone, Louisa I.	10605 West Warren	Dearborn, Mich.
Pilkington, Joseph W.	110 2nd Ave., N.	St. Petersburg, Fla.
Plager, Vernon H.	408 Marsh-Place Bldg.	Waterloo, Iowa
Postma, Edward Ynze	68 Ransom St., N. E.	Grand Rapids 2, Mich.
Preston, Francis G.	22 C. West Micheltorena	Santa Barbara, Calif.
Priddle, Harold Dwight	817 Citizens Bank Bldg.	Paducah, Ky.
Rand, Phillip	Infirmary Code No. 700, U. S. Naval Ship Yard	San Francisco, Calif.
Raphael, Sumner I.	174 Waterman St.	Providence 6, R. I.
Rauschenbach, Paul Ernest	612 East 29th St.	Paterson 4, N. J.
Redfield, William V.	1501 State Tower Bldg.	Syracuse 2, N. Y.
Rice, Glen G.	1420 Seneca	Seattle 1, Wash.
Riddle, Bedford N.	8 South Howard St.	Akron 8, Ohio
Ritzman. Thomas Alexander	5 South State St.	Concord, N. H.
Robin, Charles Murray	34 Dewey St.	Huntington, N. Y.
Robinson, David	99 Pratt St.	Hartford 3, Conn.
Roessing, Lawrence W., Jr.	1750 East 19th Ave.	Denver, Colo.
Rogers, Stanley F., Jr.	Baylor University College of Medicine	Houston 5, Texas
Rojo, Oscar Jimenez	105 South Main St.	Sheridan, Wyo.
Rose, Francis Leland	Suite 314, 300 Broadway	Camden 3, N. J.
Roth, Laurence G.	U. S. Naval Hospital	Chelsea, Mass.
Roth, Leonard	320 El Toyonal	Orinda, Calif.
Rotstein, Morris Louis	167 College St.	Toronto 2, Ont., Canada
Rowe, Daniel H.	2272 Air Base Group, Medical Squadron	Orlando, Fla.
Rowley, Thomas O.	34 North Macdonal St.	Mesa, Arizona
Rumbolz, William Leonard	1607 Medical Arts Bldg.	Omaha 2, Neb.
Rubpersberg, Anthony, Jr.	500 South Drexel Ave.	Columbus, Ohio
Sagarra, Magin	40 West 67th St.	New York 23, N. Y.
St. Amant, Alvin F.	432 Reymond Bldg.	Baton Rouge, La.
Sargent, Donald Virgil	1703 North Michigan Ave.	Saginaw, Mich.
Sargent, Edward C., Jr.	The Austin Clinic, 209 West Mill St.	Austin, Minn.
Saxe, I. Henry	65 Central Park W.	New York 23, N. Y.
Schaefer, Jane	490 Post St.	San Francisco 2, Calif.
Schecter, William J.	6061 West 3rd St.	Los Angeles 36, Calif.
Schmidt, Richard T. F.	200 Paramount Bldg.	Cincinnati 6, Ohio
Schneider, John A.	550 Grant St.	Pittsburgh 19, Pa.
Shell, James Henry, Jr.	214 Medical Arts Bldg.	Baltimore 1, Md.
Shiffler, Harry K.	804 Equitable Bldg.	Des Moines, Iowa
Sholder, Seymour	109 North Wabash Ave.	Chicago 2, Ill.
Shortle, James S.	Medical Arts Square	Albuquerque, N. Mex.
Siebert, Norman Clifford	Wichita Clinic, 3244 East Douglas	Wichita 8, Kan.
Silverman, Harold E.	100 West North Ave.	Chicago 10, Ill.
Sivitz, Howard D.	255 South 17th St.	Philadelphia 3, Pa.
Slate, Thomas A.	2107 Fifth Ave.	San Diego 1, Calif.
Smith, Benjamin F.	3720 Washington Blvd.	St. Louis 8, Mo.
Smith, Percy L.	916 West State St.	Trenton, N. J.
	(Single certification in *Obstetrics* only)	
Smith, William C.	1301 Broadway	Lubbock, Texas
Spangler, Clyde M.	255 South 17th St.	Philadelphia, Pa.
Stanley, Robert C. G.	2315 Edgmont Ave.	Chester, Pa.
Steffen, Elizabeth Allen	610 College Ave.	Racine, Wis.
Steinberg, Myron E.	Maternity Pavilion, Suite No. 5, Mount Sinai Hospital, 1176 Fifth Ave.	New York 29, N. Y.

Stevens, Clark W.	1200 Main St.	Dubuque, Iowa
Stith, James B.	U. S. Naval Hospital	Charleston, S. C.
Stout, Francis E.	Indiana University Medical Center, 1040 West Michigan St.	Indianapolis 7, Ind.
Stout, Joseph Henry, Jr.	595 East Colorado St.	Pasadena, Calif.
Sullivan, Mervyn J.	Infirmary, USNAS	Patuxent River, Md.
Swan, Bernard R.	291 Whitney Ave.	New Haven, Conn.
Tartikoff, George	900 Ocean Ave.	Brooklyn 26, N. Y.
Tenenblatt, William	U. S. Army Hospital	Fort George G. Meade, Md.
Teshima, John Y.	P. O. Box 1215, Nellis Air Force Base	Las Vegas, Nev.
Thompson, Nicholas James	522 Harries Bldg.	Dayton 2, Ohio
Thouin, Laurence G.	1133 Punchbowl St.	Honolulu 13, Hawaii
Thorn, John Codman	1636 Louisiana Ave.	New Orleans 15, La.
Tieche, Henry L.	1759 Fulton St.	Fresno, Calif.
Tierney, Thomas M.	4458 West Madison St.	Chicago 24, Ill.
Tisdale, Eben D.	114 West Buffalo St.	Ithaca, N. Y.
Tortora, John M.	One Nevins St.	Brooklyn 17, N. Y.
Trattler, Samuel Carlyle	One West 70th St.	New York 23, N. Y.
Turner, Milton	2406 Rio Grande	Austin, Texas
Ungerleider, Jerome L.	947 West 8th St.	Los Angeles 17, Calif.
Unher, Morris	74 Linwood Ave.	Buffalo 9. N. Y.
Van Meter, Ralph H.	244 West Main St.	Moorestown, N. J.
Vitsky, Maurice Sidney	2024 Monument Ave.	Richmond 20, Va.
Voulgaris, Dennis M.	105 Hawes St.	Wharton, Texas
Waddill, Samuel Frear	115 King St.	Hagerstown, Md.
Watkins, E. Lloyd	5 East Chestnut Hill Ave.	Philadelphia 18, Pa.
Watrous, Joseph Bert, Jr.	164 Chapin St.	Binghamton, N. Y.
Weber, Charles E.	U. S. Naval Hospital	Camp Pendleton, Calif.
Weigel, William Joseph	33 North Broadway	Aurora, Ill.
Weinberg, Seymour P.	704 Piedmont Ave.	Atlanta, Ga.
Weiner, Albert E.	127 A Bay State Rd.	Boston 15, Mass.
Weiner, Irwin	935 Park Avenue	New York 28, N. Y.
Wiener, Isadore David	990 Madison	Memphis, Tenn.
Wilbur, Daniel W.	22 Oakwood Rd.	Huntington, N. Y.
Wilcox, Howard L.	329 Main St.	Boonville, Mo.
Williams, Bruce F. P.	205 West 2nd St.	Duluth 2, Minn.
Williams, Philip T., Jr.	2814 West Mistletoe	San Antonio, Texas
Wilner, Irvin A.	17701 McNichols Rd., West	Detroit 35, Mich.
Wilson, Lester A., Jr.	University of Virginia Hospital	Charlottesville, Virginia
Winkelstein, Lawrence B.	1050 Park Avenue	New York 28, N. Y.
Withers, Robert W.	Suite 103, 1001 MacDill Ave.	Tampa 9, Fla.
Wolf, Howard I.	69-39 Yellowstone Blvd.	Forest Hills, Long Island, N. Y.
Wong, James T. S.	1415 Kalakaua Ave.	Honolulu, Hawaii
Wood, Eugene	508 East South Temple St.	Salt Lake City 2, Utah
Word, Buford	929 South 20th St.	Birmingham, Ala.
Zarou, George Salem	461 100th St.	Brooklyn 9, N. Y.
Zelenik, John Slowko	U. S. Army Hospital	Ft. Benning, Ga.
Ziccardi, Anthony Vincent	411 Cooper St.	Camden 2, N. J.
Zindler, Irving M.	151 East 83rd St.	New York 28, N. Y.
Jameson, John William	1574 Union St.	Schenectady 9, N. Y.

May 17, 1953. (Single certification in *Gynecology* only)

Luschinsky, Heinz L.	55 West 55th St.	New York 19, N. Y.

June 11, 1952. (Single certification in *Gynecology*)

Urology Award

The American Urological Association offers an annual award of $1,000.00 (first prize of $500.00, second prize $300.00, and third prize $200.00) for essays on the result of some clinical or laboratory research in urology. Competition shall be limited to urologists who have been in such specific practice for not more than ten years, and to men in training to become urologists.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Waldorf-Astoria, New York City, May 31—June 3, 1954.

For full particulars write the Executive Secretary, William P. Didusch, 1120 North Charles St., Baltimore, Md. Essays must be in his hands before Feb. 1, 1954.

First Annual Meeting, Inter-Society Cytology Council

The first annual meeting of the Inter-Society Cytology Council will be held in Philadelphia, Nov. 19 and 20, 1953.

PAUL F. FLETCHER, SECRETARY,
634 N. GRAND BLVD.
ST. LOUIS 3, MO.